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Arthritis Care & Research
Vol. 73, No. 7, July 2021, pp 924–939
DOI 10.1002/acr.24596
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2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

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Objective. To develop updated guidelines for the pharmacologic management of rheumatoid arthritis.

Methods. We developed clinically relevant population, intervention, comparator, and outcomes (PICO) questions. After conducting a systematic literature review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the certainty of evidence. A voting panel comprising clinicians and patients achieved consensus on the direction (for or against) and strength (strong or conditional) of recommendations.

Results. The guideline addresses treatment with disease-modifying antirheumatic drugs (DMARDs), including conventional synthetic DMARDs, biologic DMARDs, and targeted synthetic DMARDs, use of glucocorticoids, and use of DMARDs in certain high-risk populations (i.e., those with liver disease, heart failure, lymphoproliferative disorders, previous serious infections, and nontuberculous mycobacterial lung disease). The guideline includes 44 recommendations (7 strong and 37 conditional).

Conclusion. This clinical practice guideline is intended to serve as a tool to support clinician and patient decision-making. Recommendations are not prescriptive, and individual treatment decisions should be made through a shared decision-making process based on patients' values, goals, preferences, and comorbidities.

The findings and conclusions herein are those of the authors and do not represent the official position of the Centers for Disease Control and Prevention. This study did not involve human subjects, and therefore, approval from Human Studies Committees was not required.

This article is published simultaneously in *Arthritis & Rheumatology*.
Supported by the American College of Rheumatology.

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INTRODUCTION

To support high-quality clinical care, the American College of Rheumatology (ACR) regularly updates clinical practice guidelines for the management of rheumatoid arthritis (RA), with the most recent update reported in 2015 (1). The current recommendations address treatment with the following: 1) conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs); 2) glucocorticoids; and 3) use of these medications in certain high-risk populations. The use of vaccines and nonpharmacologic treatment approaches (although initially part of this project) will be covered in future ACR treatment guideline publications. For recommendations regarding pretreatment screening and routine laboratory monitoring, we refer readers to the 2008, 2012, and 2015 guidelines (1–3), with newly approved therapies following the screening process recommended for other medications in the same class. Recommendations for the perioperative management of patients undergoing elective orthopedic surgery are addressed in the 2017 guideline for perioperative management (4). For recommendations regarding reproductive health, we refer readers to the 2020 ACR Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases (5).

In keeping with the Grading of Recommendations Assessment, Development and Evaluation [GRADE] methodology), the ACR panel developed recommendations for commonly encountered clinical scenarios (6–8). Both ***strong*** and ***conditional*** recommendations required achieving a 70% level of agreement by the voting panel. Each recommendation is qualified as being strong or conditional. In this context, strong recommendations are those for which the panel is highly confident that the recommended option favorably balances the expected benefits and risks for the majority of patients in clinical practice. In contrast, conditional recommendations are those for which the panel is less confident that the potential benefits outweigh the risks. A recommendation can be conditional either because of low or very low certainty in the evidence supporting one option over another, or because of an expectation of substantial variations in patient preferences for the options under consideration.

METHODS

This guideline follows the ACR guideline development process and ACR policy guiding the management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) (6,8), which includes GRADE methodology (6,8), and abides by the AGREE Reporting Checklist to ensure the completeness and transparency of reporting in practice guidelines (9). Supplementary Appendix 1, available on the *Arthritis Care & Research* website at http://onlin

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Submitted for publication September 8, 2020; accepted in revised form March 15, 2021.

elibrary.wiley.com/doi/10.1002/acr.24596/abstract), includes a detailed description of the methods. Briefly, the core leadership team drafted clinical population, intervention, comparator, and outcomes (PICO) questions. The literature review team performed systematic literature reviews for the PICO questions, selected and evaluated individual studies and graded the quality of the body of evidence available for each outcome, and produced the evidence report that summarizes these assessments (see Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract). The core team defined the critical study outcome as disease activity for most PICO questions. Because the ACR has, in a separate project, endorsed several disease activity measures for use in clinical practice, this guideline does not define levels of disease activity or the instruments a clinician should use to measure it (10). For PICO questions related to tapering, the critical outcomes were disease flare and subsequent return to the treatment target. Physical function, radiographic progression, quality of life, other patient-reported outcome measures, and adverse events were defined as important outcomes. Additional clinical outcomes were defined for PICO questions pertaining to select high-risk conditions (see Supplementary Appendix 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract). When available, cost-effectiveness studies were included with the evidence reports. Cost estimates (average wholesale prices) were retrieved from Lexicomp (see Supplementary Appendix 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract). The panel considered these estimates from a societal perspective, i.e., based on the list price, and not the copay.

An in-person panel of 10 patients with RA, moderated by the project's principal investigator, reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives for consideration by the voting panel. The voting panel (13 clinicians and 2 patients) reviewed the evidence reports and patient perspectives and voted on recommendation statements. Rosters of the core leadership, literature review team, and panel members are listed in Supplementary Appendix 5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract.

Several guiding principles, definitions, and assumptions were established a priori (Table 1). Because poor prognostic factors (11) have had less impact than other factors on prior RA treatment recommendations, they were not explicitly considered in formulating the PICO questions. However, poor prognostic factors were considered as possible influential factors in physicians' and patients' decision-making when developing recommendations. In contrast to the 2015 guideline (1), recommendations were not provided for subgroups defined by early versus late RA disease duration. This change was made because current disease activity, prior therapies used, and the presence of comorbidities were felt to be more relevant than disease duration for most treatment decisions. However, early diagnosis and treatment in RA is associated with improved outcomes and is thus an important overarching principle in its management (12). Recommendations are intended for the general RA patient population and assume that patients do not have contraindications to the options under consideration.

Table 1. Guiding principles*

RA requires early evaluation, diagnosis, and management.
Treatment decisions should follow a shared decision-making process.
Treatment decisions should be reevaluated within a minimum of 3 months based on efficacy and tolerability of the DMARD(s) chosen.
Disease activity levels refer to those calculated using RA disease activity measures endorsed by the ACR (10).
Recommendations are intended for the general RA patient population and assume that patients do not have contraindications to the options under consideration.
Recommendations are limited to DMARDs approved by the US FDA for treatment of RA. csDMARDs: hydroxychloroquine, sulfasalazine, methotrexate, leflunomide bDMARDs: TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab)† tsDMARDs: JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide.
Serious infection refers to an infection requiring intravenous antibiotics or hospitalization.
Biosimilars are considered equivalent to FDA-approved originator bDMARDs.
Recommendations referring to bDMARDs exclude rituximab unless patients have had an inadequate response to TNF inhibitors (in order to be consistent with FDA approval) or have a history of lymphoproliferative disorder for which rituximab is an approved therapy.
Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modification of treatment to minimize disease activity with the goal of reaching a predefined target (low disease activity or remission).
Target refers to low disease activity or remission.
Recommendations specify that patients be at target (low disease activity or remission) for at least 6 months prior to tapering.
Dose reduction refers to lowering the dose or increasing the dosing interval of a DMARD. Gradual discontinuation of a DMARD is defined as gradually lowering the dose of a DMARD and subsequently stopping it.

* RA = rheumatoid arthritis; DMARDs = disease-modifying antirheumatic drugs; ACR = American College of Rheumatology; FDA = Food and Drug Administration; csDMARDs = conventional DMARDs; bDMARDs = biologic DMARDs; TNF = tumor necrosis factor; IL-6 = interleukin-6; tsDMARDs = targeted synthetic DMARDs.
† Anakinra was not included due to infrequent use for patients with RA.

RESULTS/RECOMMENDATIONS

The recommendations are based on a set of 81 PICO questions. The literature review initially identified 22,971 manuscripts (for the full set of PICO questions covering both pharmacologic and nonpharmacologic treatment). After excluding 18,333 titles

and abstracts, 4,038 full-text articles were screened, of which 1,392 were excluded and 2,646 were considered for the evidence report. After full-text screening, 133 manuscripts were mapped to ≥1 PICO questions addressing pharmacologic treatment (see Supplementary Appendix 6, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract). The literature review did not identify any evidence for 41% (n = 33) of the PICO questions.

Recommendations for DMARD-naive patients with moderate-to-high disease activity (Table 2)

DMARD monotherapy

Methotrexate is strongly recommended over hydroxychloroquine or sulfasalazine for DMARD-naive patients with moderate-to-high disease activity

This recommendation is strongly in favor of methotrexate despite very low-certainty evidence for hydroxychloroquine and low-certainty evidence for sulfasalazine based on the amount of data supporting the disease-modifying properties of methotrexate monotherapy compared to hydroxychloroquine or sulfasalazine and concerns over the long-term tolerability of sulfasalazine (13,14).

Methotrexate is conditionally recommended over leflunomide for DMARD-naive patients with moderate-to-high disease activity

Despite low-certainty evidence of comparable efficacy, methotrexate is preferred over leflunomide because of the evidence supporting its value as an anchor DMARD in combination regimens. Additional advantages of methotrexate include its greater dosing flexibility and lower cost.

Methotrexate monotherapy is strongly recommended over bDMARD or tsDMARD monotherapy for DMARD-naive patients with moderate-to-high disease activity

There is low-certainty evidence suggesting superiority of tocilizumab monotherapy (15) over methotrexate monotherapy and moderate-certainty evidence suggesting greater efficacy

Table 2. Disease-modifying antirheumatic drugs (DMARDs) initiation*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)†	Evidence table(s), in Supp. App. 2
Initiation of treatment in DMARD-naive patients with moderate-to-high disease activity			
Methotrexate monotherapy is **strongly** recommended over:			
Hydroxychloroquine or sulfasalazine	Very low/low‡	PICO 2a.C1/C2	p. 14–5
bDMARD or tsDMARD monotherapy	Very low/moderate	PICO 5a.C1–4/C5§	p. 61–78
Combination of methotrexate plus a non–TNF inhibitor bDMARD or tsDMARD¶	Low/very low	PICO 6a.C2–4/C5§	p. 109, 117–28
Methotrexate monotherapy is **conditionally** recommended over:			
Leflunomide	Low	PICO 2a.C3	p. 18
Dual or triple csDMARD therapy¶	Moderate	PICO 4a.C1–C2	p. 46–9
Combination of methotrexate plus a TNF inhibitor¶	Low	PICO 6a.C1	p. 110
Initiation of a csDMARD without short-term (<3 months) glucocorticoids is **conditionally** recommended over initiation of a csDMARD with short-term glucocorticoids.	Very low	PICO 7a	p. 167
Initiation of a csDMARD without longer-term (≥3 months) glucocorticoids is **strongly** recommended over initiation of a csDMARD with longer-term glucocorticoids.	Moderate	PICO 8a	p. 170
Initiation of treatment in DMARD-naive patients with low disease activity			
Hydroxychloroquine is **conditionally** recommended over other csDMARDs.	Very low	PICO 1a.C1–4	p. 1–6
Sulfasalazine is **conditionally** recommended over methotrexate.	Very low	PICO 1a.C2	p. 2
Methotrexate is **conditionally** recommended over leflunomide.	Very low	PICO 1a.C3	p. 5
Initiation of treatment in csDMARD-treated, but methotrexate-naive, patients with moderate-to-high disease activity#			
Methotrexate monotherapy is **conditionally** recommended over the combination of methotrexate plus a bDMARD or tsDMARD.**	Moderate/very low	PICO 6b.C1–4/C5§	p. 136–56

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD; TNF = tumor necrosis factor; csDMARD = conventional synthetic DMARD.
† The closest matching PICO questions to each recommendation are provided.
‡ The first certainty of evidence applies to the first listed option; the second certainty of evidence applies to the second listed option.
§ The original PICO included individual DMARDs as comparators. The recommendation considers bDMARDs as a group.
¶ The direction of the beneficial effect is in favor of the nonpreferred option.
# Other recommendations for this patient population are the same as those for DMARD-naive patients.
** The direction of the beneficial effect is in favor of the nonpreferred option. The certainty of evidence is high for the combination of methotrexate plus a TNF inhibitor and moderate for other bDMARDs.

of JAK inhibitor monotherapy over methotrexate monotherapy. The study by van Vollenhoven et al (16) was not considered by the voting panel as it was published after the evidence report was updated. However, methotrexate monotherapy is preferred because of its established efficacy and safety as a first-line DMARD and low cost. Moreover, tocilizumab and JAK inhibitors are not approved by the US Food and Drug Administration (FDA) for use in csDMARD-naive patients. Safety concerns released in early 2021 associated with JAK inhibitors (17,18) further support the recommendation of methotrexate monotherapy over tsDMARDs as initial DMARD therapy at this time.

Methotrexate monotherapy is conditionally recommended over dual or triple csDMARD therapy for DMARD-naive patients with moderate-to-high disease activity

The recommendation favors methotrexate monotherapy because the higher burden of combination therapy (e.g., multiple medications, higher cost) outweighs the moderate-quality evidence suggesting greater improvements in disease activity associated with combination csDMARDs (19). The recommendation is conditional because some patients may choose csDMARD combination therapy for an increased probability of obtaining a better response despite the added burden of taking multiple medications.

Methotrexate monotherapy is conditionally recommended over methotrexate plus a tumor necrosis factor (TNF) inhibitor for DMARD-naive patients with moderate-to-high disease activity

Despite low-certainty evidence supporting greater improvement in disease activity with methotrexate plus a TNF inhibitor, methotrexate monotherapy is preferred over the combination because many patients will reach their goal on methotrexate monotherapy and because of the additional risks of toxicity and higher costs associated with TNF inhibitors. The recommendation is conditional because some patients, especially those with poor prognostic factors, may prioritize more rapid onset of action and greater chance of improvement associated with combination therapy (20–22) over the additional risks and costs associated with initial use of methotrexate in combination with a TNF inhibitor.

Methotrexate monotherapy is strongly recommended over methotrexate plus a non–TNF inhibitor bDMARD or tsDMARD for DMARD-naive patients with moderate-to-high disease activity

There is very low-certainty evidence supporting the superiority of methotrexate plus a non–TNF inhibitor bDMARD or tsDMARD over methotrexate monotherapy in DMARD-naive patients; thus, methotrexate monotherapy is strongly preferred given the lack of proven benefit and additional risks and costs associated with the addition of a non–TNF inhibitor bDMARD or tsDMARD in this patient population.

Glucocorticoids

Initiation of a csDMARD without short-term (<3 months) glucocorticoids is conditionally recommended over initiation of a csDMARD with short-term glucocorticoids for DMARD-naive patients with moderate-to-high disease activity

While the voting panel agreed that glucocorticoids should not be systematically prescribed, the recommendation is conditional because all members acknowledged that short-term glucocorticoids are frequently necessary to alleviate symptoms prior to the onset of action of DMARDs. Treatment with glucocorticoids should be limited to the lowest effective dose for the shortest duration possible. The toxicity associated with glucocorticoids was judged to outweigh potential benefits.

Initiation of a csDMARD without longer-term (≥3 months) glucocorticoids is strongly recommended over initiation of a csDMARD with longer-term glucocorticoids for DMARD-naive patients with moderate-to-high disease activity

Although some patients may require longer-term glucocorticoids, this strong recommendation *against* longer-term glucocorticoid therapy is made because of its significant toxicity.

Recommendations for DMARD-naive patients with low disease activity (Table 2)

Hydroxychloroquine is conditionally recommended over other csDMARDs, sulfasalazine is conditionally recommended over methotrexate, and methotrexate is conditionally recommended over leflunomide for DMARD-naive patients with low disease activity

Hydroxychloroquine is conditionally recommended over other csDMARDs because it is better tolerated and has a more favorable risk profile in patients with RA. Sulfasalazine is recommended over methotrexate because it is less immunosuppressive, and the patient panel felt that many patients with low disease activity would prefer to avoid the side effects associated with methotrexate. The recommendations are conditional because methotrexate may be the preferred initial therapy in patients at the higher end of the low disease activity range and in those with poor prognostic factors (11). Methotrexate is recommended over leflunomide because of its greater dosing flexibility and lower cost.

Recommendation for patients who have been treated with csDMARDs, excluding methotrexate, and who have moderate-to-high disease activity (Table 2)

Recommendations are the same as for DMARD-naive patients except for this population. The strength of the following recommendation is conditional for all bDMARDs and tsDMARDs.

Methotrexate monotherapy is conditionally recommended over the combination of methotrexate plus a bDMARD or tsDMARD

The recommendation is conditional because the voting panel thought that some patients who have already had persistent disease activity despite use of ≥1 csDMARD will prefer combination treatment for a more rapid response.

Recommendations for administration of methotrexate (Table 3)

Oral methotrexate is conditionally recommended over subcutaneous methotrexate for patients initiating methotrexate

Oral administration is preferred, despite moderate evidence suggesting superior efficacy of subcutaneous injections, due to the ease of oral administration and similar bioavailability at typical starting doses (23).

Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks is conditionally recommended over initiation/titration to a weekly dose of <15 mg

The recommendation is conditional because there are few studies comparing different dosing strategies and wide variation in physician and patient preferences regarding the tradeoff between the increased efficacy and risks of toxicity associated with higher starting doses. This recommendation refers only to the initial prescribing of methotrexate and is not meant to limit further dose escalation, which often provides additional efficacy (24).

A split dose of oral methotrexate over 24 hours or weekly subcutaneous injections, and/or an increased dose of folic/folinic acid, is conditionally recommended over switching to alternative DMARD(s) for patients not tolerating oral weekly methotrexate

Despite the very low certainty of evidence supporting these strategies for alleviating side effects related to methotrexate, split dosing, changing to the subcutaneous route of administration, and increased doses of folic/folinic acid are the preferred initial strategies over switching to another DMARD because of the efficacy, long-term safety, and low costs associated with methotrexate. The recommendation is conditional because patient preferences play an important role in the decision whether to continue methotrexate or switch to other DMARDs.

Switching to subcutaneous methotrexate is conditionally recommended over the addition of/switching to alternative DMARD(s) for patients taking oral methotrexate who are not at target

This recommendation is consistent with the voting panel's overarching principle of maximizing use of methotrexate prior to switching/adding DMARDs. However, there are no data comparing outcomes in patients who switch to subcutaneous methotrexate versus another treatment strategy that includes other DMARDs. The recommendation is conditional because patient preferences and the magnitude of previous response to methotrexate play an important role in this decision.

Table 3. Methotrexate administration*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Oral methotrexate is **conditionally** recommended over subcutaneous methotrexate for patients initiating methotrexate.	Moderate	PICO 9	p. 181
Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks is **conditionally** recommended over initiation/titration to a weekly dose of <15 mg.†	Moderate/ very low‡	PICO 10.C1–C3	p. 184–5
A split dose of oral methotrexate over 24 hours or subcutaneous injections, and/or an increased dose of folic/folinic acid, is **conditionally** recommended over switching to alternative DMARD(s) for patients not tolerating oral weekly methotrexate.	Very low	PICO 16 and PICO 15	p. 206–10
Switching to subcutaneous methotrexate is **conditionally** recommended over the addition of/switching to alternative DMARD(s) for patients taking oral methotrexate who are not at target.	Very low	PICO 18	p. 235

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; DMARD = disease-modifying antirheumatic drug.
† This recommendation refers only to the initial prescribing of methotrexate and is not meant to limit further dose escalation, which often provides additional efficacy.
‡ The first certainty of evidence applies to the first listed option; the second certainty of evidence applies to the second option.

Recommendations for treatment modification in patients treated with DMARDs who are not at target (Table 4)

Treat-to-target

A treat-to-target approach is strongly recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs

This recommendation applies to dose optimization of methotrexate and to the subsequent addition of DMARDs when required. The recommendation is strong despite low-certainty evidence because of the recognized importance of systematic monitoring and adjustment of treatment to minimize inflammation to prevent joint damage, as well as other long-term sequelae including cardiovascular disease and osteoporosis.

A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs

The recommendation is conditional because of the uncertain incremental benefits of treat-to-target over usual care in this patient population. In this context, usual care refers to commonly employed practice patterns, i.e., adjustment of treatment based on shared decision-making, albeit typically without systematic monitoring of disease activity using validated measures to reach a predefined target. Moreover, 1) the number of remaining available treatment options, 2) the impact of noninflammatory causes of pain, comorbidities, and/or damage on the accuracy of validated disease activity assessments, and 3) the patient's threshold for changing medications may have a more significant influence on the decision to follow a treat-to-target approach in this population compared to patients who are bDMARD- and tsDMARD-naive.

A minimal initial treatment goal of low disease activity is conditionally recommended over a goal of remission

An initial target of low disease activity is preferred because remission by established criteria may not be achievable for many patients (25). In addition, the patient panel emphasized that failure to reach a specified target may be disheartening and stressful for some patients. They emphasized that it would be preferable to *initially* aim for low disease activity and *subsequently* consider a goal of remission. However, treatment goals should be systematically reassessed over time and individualized to each patient to ensure that remission is targeted when possible. The recommendation is conditional because remission is a reasonable initial goal for patients with early disease and minimal exposure to bDMARDs and tsDMARDs, and patient preferences play a significant role in this decision.

Modification of DMARD(s)

Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine) for patients taking maximally tolerated doses of methotrexate who are not at target

The panel vigorously debated whether to recommend addition of a bDMARD or tsDMARD versus sulfasalazine and

Table 4. Treatment modification*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
A TTT approach is **strongly** recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs.	Low	PICO 12.a	p. 191
A TTT approach is **conditionally** recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs.	Very low	PICO 12.b	p. 199
A minimal initial treatment goal of low disease activity is **conditionally** recommended over a goal of remission.	Low	PICO 13	p. 201
Addition of a bDMARD or tsDMARD is **conditionally** recommended over triple therapy for patients taking maximally tolerated doses of methotrexate who are not at target.	Very low	PICO 19.C2–C6†	p. 240–1
Switching to a bDMARD or tsDMARD of a different class is **conditionally** recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target.	Very low	PICO 24–27†	p. 293–338
Addition of/switching to DMARDs is **conditionally** recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target.	Very low	PICO 23	p. 292
Addition of/switching to DMARDs (with or without IA glucocorticoids) is **conditionally** recommended over the use of IA glucocorticoids alone for patients taking DMARDs who are not at target.	Very low	PICO 28.C1–C2	p. 339–40

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; TTT = treat-to-target; bDMARDs = biologic disease-modifying antirheumatic drugs; tsDMARDs = targeted synthetic DMARDs; IA = intraarticular.
† The original PICO included individual DMARDs as comparators. The recommendation considers bDMARDs as a group.

hydroxychloroquine (triple therapy) for patients with an inadequate response to methotrexate monotherapy in view of very low-certainty evidence favoring bDMARDs or tsDMARDs, randomized controlled trials demonstrating equivalent long-term outcomes across both treatment strategies, and significantly less societal cost associated with triple therapy (26–29). Addition of a bDMARD or tsDMARD was ultimately preferred because the patient panel strongly prioritized maximizing improvement as quickly as possible. In addition, both the patient and voting panels valued the greater persistence of methotrexate plus a bDMARD or tsDMARD compared to triple therapy (defined in Table 1) (13,30). The recommendations from these studies (13,31) are conditional because triple therapy may be preferred in lower resource settings as well as in patients with specific comorbidities for whom triple therapy may be associated with significantly less risk of adverse events. This choice is highly preference sensitive, and decisions on how best to escalate care should incorporate patients' preferences. There is no current recommendation for a bDMARD versus a tsDMARD when adjusting treatment; however, the voting panel acknowledged that safety data released in early 2021 (17,18) may require a modification of this recommendation when peer-reviewed results are published.

Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target

The recommendation is based on very low-certainty evidence supporting greater improvement in disease activity and drug survival among patients switching classes. The recommendation is conditional because patient and physician preferences are likely to vary based on prior experiences with specific DMARDs.

Use of glucocorticoids

Addition of/switching to DMARDs is conditionally recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target

This recommendation assumes that improved disease control with DMARDs should allow less use of glucocorticoids. The recommendation is conditional because the continued use of glucocorticoids may be required for patients who do not respond to DMARDs even after maximizing methotrexate dosage and switching DMARD classes.

Addition of/switching to DMARDs (with or without intraarticular [IA] glucocorticoids) is conditionally recommended over the use of IA glucocorticoids alone for patients taking DMARDs who are not at target

This recommendation was based on the premise that DMARDs should be adjusted to reduce disease activity, irrespective of treatment with IA glucocorticoids. The recommendation is conditional because patients may choose to defer adding/switching DMARDs if they obtain relief from IA injection(s).

Recommendations for tapering/discontinuing DMARDs (Table 5)

Because of the moderate-to-high risk for flare and the potential for irreversible long-term damage associated with stopping all DMARDs, the following recommendations presume that patients maintain a therapeutic dose of at least 1 DMARD. In addition, the recommendations specify that patients be at target (low disease activity or remission) for at least 6 months

Table 5. Tapering disease-modifying antirheumatic drugs (DMARDs)*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Continuation of all DMARDs at their current dose is **conditionally** recommended over a dose reduction of a DMARD.	Low	PICO 54.a	p. 381
Dose reduction is **conditionally** recommended over gradual discontinuation of a DMARD.	Low	PICO 52.C2 and PICO 53. C2	p. 351–5, p. 372–6
Gradual discontinuation is **conditionally** recommended over abrupt discontinuation of a DMARD.	Low	PICO 52.C1 and PICO 53.C1	p. 351, 372
Gradual discontinuation of sulfasalazine is **conditionally** recommended over gradual discontinuation of hydroxychloroquine for patients taking triple therapy who wish to discontinue a DMARD.	Very low	PICO 58	p. 400
Gradual discontinuation of methotrexate is **conditionally** recommended over gradual discontinuation of the bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD.	Very low	PICO 59.C1	p. 401

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD.

prior to tapering. Patients in remission for <6 months should not routinely be considered for dose reduction or withdrawal. Although the optimal time at target prior to tapering has not been established, the voting panel considered 6 months to be a reasonable minimal length of time to ensure stable disease control. "Dose reduction" refers to lowering the dose or increasing the dosing interval of a DMARD. "Gradual discontinuation" denotes gradually lowering the dose of a DMARD and subsequently stopping it.

Continuation of all DMARDs at their current dose is conditionally recommended over a dose reduction of a DMARD, dose reduction is conditionally recommended over gradual discontinuation of a DMARD, and gradual discontinuation is conditionally recommended over abrupt discontinuation of a DMARD for patients who are at target for at least 6 months

These recommendations are based on studies demonstrating a higher risk of flare in patients who are 1) lowering the dose of a DMARD versus continuing DMARDs at the same dose, and 2) abruptly versus gradually discontinuing a DMARD (32–36). The recommendations are conditional because patient and physician preferences are expected to vary.

Gradual discontinuation of sulfasalazine is conditionally recommended over gradual discontinuation of hydroxychloroquine for patients taking triple therapy who wish to discontinue a DMARD

Gradually discontinuing sulfasalazine is recommended because of its poorer treatment persistence due to adverse events (14). The recommendation is conditional because patient and physician preferences are expected to vary.

Gradual discontinuation of methotrexate is conditionally recommended over gradual discontinuation of the bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD

In the absence of direct evidence, gradually discontinuing methotrexate is preferred because a bDMARD or tsDMARD is typically added following an inadequate response to methotrexate. Thus, the continued use of the bDMARD or tsDMARD is more likely to maintain disease control than the continued use of methotrexate. The recommendation is conditional because gradual discontinuation of the bDMARD or tsDMARD may be favored depending on comorbidities, risk for infection, cost concerns, as well as patient and clinician preferences. The voting panel cautioned that many patients treated with certain monoclonal antibodies may require ongoing treatment with methotrexate to prevent the formation of antidrug antibodies (37).

Recommendations for specific patient populations (Table 6)

Subcutaneous nodules

Methotrexate is conditionally recommended over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity

Switching to a non-methotrexate DMARD is conditionally recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules

While accelerated nodulosis has been observed in patients starting methotrexate (38), there are no studies examining comparative strategies for patients with stable or progressive subcutaneous nodules. The preceding 2 recommendations are conditional because patient and clinician preferences are expected to vary. The recommendation to switch is based on the premise that methotrexate is a contributing factor to progressive nodulosis.

Pulmonary disease

Methotrexate is conditionally recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease, or incidental disease detected on imaging, who have moderate-to-high disease activity

Studies indicate that preexisting lung disease is a risk factor for methotrexate-related pneumonitis (39,40). However, the overall risk of worsening lung disease attributable to methotrexate is uncertain, and alternative DMARDs have also been associated with lung disease (41–45). The recommendation is in favor of methotrexate because of its important role as an anchor treatment in RA and the lack of alternatives with similar efficacy and/or superior long-term safety profiles. The recommendation is conditional because some clinicians (rheumatologists and pulmonologists) and patients will prefer an alternative option rather than accept any additional risk of lung toxicity. Patients with preexisting lung disease should be informed of their increased risk of methotrexate pneumonitis prior to initiating treatment with methotrexate.

Table 6. Specific patient populations*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Subcutaneous nodules			
Methotrexate is **conditionally** recommended over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity.	Very low	PICO 64	p. 427
Switching to a non-methotrexate DMARD is **conditionally** recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules.	Very low	PICO 65	p. 428
Pulmonary disease			
Methotrexate is **conditionally** recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease who have moderate-to-high disease activity.	Very low	PICO 67	p. 430
Heart failure			
Addition of a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over addition of a TNF inhibitor for patients with NYHA class III or IV heart failure and an inadequate response to csDMARDs.	Very low	PICO 70	p. 435
Switching to a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over continuation of a TNF inhibitor for patients taking a TNF inhibitor who develop heart failure.	Very low	PICO 71	p. 436
Lymphoproliferative disorder			
Rituximab is **conditionally** recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity.	Very low	PICO 75 and PICO 76	p. 446–7
Hepatitis B infection			
Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status).	Very low	PICO 82	p. 459
Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive.	Very low	PICO 83	p. 464
Frequent monitoring alone is **conditionally** recommended over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative.	Very low	PICO 84	p. 471
Nonalcoholic fatty liver disease			
Methotrexate is **conditionally** recommended over alternative DMARDs for DMARD-naive patients with nonalcoholic fatty liver disease, normal liver enzymes and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to high disease activity.	Very low	PICO 87	p. 489
Persistent hypogammaglobulinemia without infection			
In the setting of persistent hypogammaglobulinemia without infection, continuation of rituximab therapy for patients at target is **conditionally** recommended over switching to a different bDMARD or tsDMARD.	Very low	PICO 66	p. 429
Previous serious infection			
Addition of csDMARDs is **conditionally** recommended over addition of a bDMARD or tsDMARD for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity despite csDMARD monotherapy.	Very low	PICO 88	p. 490
Addition of/switching to DMARDs is **conditionally** recommended over initiation/dose escalation of glucocorticoids for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity.	Very low	PICO 90 and PICO 91	p. 496–7
Nontuberculous mycobacterial lung disease			
Use of the lowest possible dose of glucocorticoids (discontinuation if possible) is **conditionally** recommended over continuation of glucocorticoids for patients with nontuberculous mycobacterial lung disease.	Very low	No relevant PICO	
Addition of csDMARDs is **conditionally** recommended over addition of a bDMARD or tsDMARD for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARD monotherapy.	Very low	PICO 92	p. 498
Abatacept is **conditionally** recommended over other bDMARDs and tsDMARDs for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARDs.	Very low	PICO 93	p. 499

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; DMARDs = disease-modifying antirheumatic drugs; TNF = tumor necrosis factor; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD; NYHA = New York Heart Association; csDMARDs = conventional synthetic DMARDs.

Table 7. Key clinical questions requiring further research*

Methotrexate administration
At what dose and route of administration should methotrexate be started?
Does switching to non-methotrexate DMARDs improve tolerability over increasing the dose of folic acid, or using folinic acid or using split dose or subcutaneous dosing, for RA patients with side effects when taking methotrexate?
TTT
What is the efficacy of TTT in different patient populations (early versus late, bDMARD- or tsDMARD-exposed, elderly-onset, comorbidities)?
What is the optimal target and method of assessment of disease activity for TTT in different populations?
Comparative effectiveness/safety
What is the comparative effectiveness/safety between bDMARDs and tsDMARDs?
What is the comparative effectiveness/safety between adding bDMARDs or tsDMARDs to methotrexate and switching to bDMARD or tsDMARD monotherapy?
What is the comparative effectiveness/safety between TTT by maximizing use of methotrexate (i.e., escalating dose via subcutaneous route) and adding/switching to bDMARD or tsDMARD monotherapy?
When, which, and how should DMARDs be tapered/discontinued?
Do clinical or biologic markers predict a differential response to DMARDs?
Comorbidities
What is the effectiveness/safety of alternative treatment strategies in RA patients with clinical lung disease or NAFLD?
Which DMARDs can be initiated or continued after receiving checkpoint inhibitor therapy?
Which DMARDs should be used in patients with solid malignancies, including skin cancer?
Is there a time frame before which DMARDs can be started/resumed in patients with concomitant solid malignancies?

* DMARDs = biologic disease-modifying antirheumatic drugs; RA = rheumatoid arthritis; TTT = treat-to-target; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD; NAFLD = nonalcoholic fatty liver disease.

Heart failure

Addition of a non–TNF inhibitor bDMARD or tsDMARD is conditionally recommended over addition of a TNF inhibitor for patients with New York Heart Association (NYHA) class III or IV heart failure and an inadequate response to csDMARDs

Switching to a non–TNF inhibitor bDMARD or tsDMARD is conditionally recommended over continuation of a TNF inhibitor for patients taking a TNF inhibitor who develop heart failure

These recommendations are based on the risk of worsening heart failure observed in randomized clinical trials of TNF inhibitors in patients with NYHA class III or IV heart failure without RA (46,47). Both recommendations are conditional because of the very low-certainty evidence supporting these PICO questions.

Lymphoproliferative disorder

Rituximab is conditionally recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity

Rituximab is preferred over other DMARDs, regardless of previous DMARD experience, because it would not be expected to increase the risk of recurrence or worsening of these lymphoproliferative disorders. The recommendation is conditional because of the very low-certainty evidence supporting this PICO question.

Hepatitis B infection

Prophylactic antiviral therapy is strongly recommended over frequent monitoring of viral load and liver enzymes alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status)

Prophylactic antiviral therapy is strongly recommended over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive

Frequent monitoring alone of viral load and liver enzymes is conditionally recommended over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative

These recommendations were made based on the risk of hepatitis B reactivation due to core antibody and surface antigen status and the specific DMARD being initiated and are consistent with the updated American Association for the Study of Liver Diseases guidance (48). Patients at risk for hepatitis B reactivation should be comanaged with a hepatologist. The third recommendation is conditional because it is less certain whether the benefit of prophylactic antiviral therapy outweighs the risks and cost of this treatment in the specified patient population.

Nonalcoholic fatty liver disease (NAFLD)

Methotrexate is conditionally recommended over alternative DMARDs for DMARD-naive patients with NAFLD, normal liver enzymes and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to-high disease activity

Given the concerns about the risk of hepatotoxicity associated with methotrexate therapy in patients with NAFLD, use of methotrexate should be restricted to patients with normal liver enzymes and liver function tests and without evidence of liver disease or liver fibrosis (Stage 3 or 4). Noninvasive testing to diagnose and stage liver fibrosis as well as consultation with a gastroenterologist or hepatologist should be considered in patients prior to initiating methotrexate (49). In addition, more frequent monitoring should be performed in this patient population (every 4 to 8 weeks). The recommendation is conditional because patients' and clinicians' risk tolerance varies.

Persistent hypogammaglobulinemia without infection

In the setting of persistent hypogammaglobulinemia without infection, continuation of rituximab therapy for patients at target is conditionally recommended over switching to a different bDMARD or tsDMARD

Continuing rituximab in patients who are at target is preferred because of the uncertain clinical significance of hypogammaglobulinemia in patients without infection. Although an increased risk of infection has been described in RA patients with hypogammaglobulinemia, it is not known if a switch in DMARDs in patients who are at target is more effective in lowering infection risk while maintaining disease control than continuation of rituximab. The recommendation is conditional because physician and patient risk tolerance is likely to vary depending on the degree of hypogammaglobulinemia and patient-specific risk factors for infection.

Previous serious infection

Addition of csDMARDs is conditionally recommended over addition of a bDMARD or tsDMARD for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity despite csDMARD monotherapy

This conditional recommendation is made based on observational data suggesting a lower risk of infection associated with combination csDMARDs (dual or triple therapy) compared to bDMARDs or tsDMARDs (50). Some clinicians may prefer csDMARDs even if the serious infection occurred >12 months prior to considering a change.

Addition of/switching to DMARDs is conditionally recommended over initiation/dose escalation of glucocorticoids for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity

This conditional recommendation is made based on observational studies suggesting a strong association between dose and duration of glucocorticoids with the risk of serious infection (51–53).

Nontuberculous mycobacterial (NTM) lung disease

Given the variability of NTM lung disease severity and response to treatment, patients should be closely comanaged with an infectious disease or pulmonary specialist.

Use of the lowest possible dose of glucocorticoids (discontinuation if possible) is conditionally recommended over continuation of glucocorticoids without dose modification for patients with NTM lung disease

This recommendation is based on studies suggesting an increased risk of NTM lung disease in patients receiving either inhaled or oral glucocorticoids (54,55).

Addition of csDMARDs is conditionally recommended over addition of a bDMARD or tsDMARD for patients with NTM lung disease who have moderate-to-high disease activity despite csDMARD monotherapy

This recommendation is based on the lower expected risk of NTM lung disease associated with csDMARDs compared to bDMARDs and tsDMARDs (56).

Abatacept is conditionally recommended over other bDMARDs and tsDMARDs for patients with NTM lung disease who have moderate-to-high disease activity despite csDMARDs

Abatacept is conditionally recommended over other bDMARDs and tsDMARDs based on population data extrapolated from studies on tuberculosis (57). There is considerable uncertainty regarding the risk of mycobacterial infections associated with non–TNF inhibitor bDMARDs and tsDMARDs; however, TNF inhibitors are associated with increased rates of mycobacterial infections and should be avoided (58).

The preceding 3 recommendations are conditional because of the very low-certainty evidence supporting the analysis of the differences in treatment outcomes posed by these PICO questions.

DISCUSSION

The ACR guidelines were developed to provide clinicians with recommendations for decisions frequently faced in clinical practice. Several new topics are included in this update, including recommendations for administration of methotrexate, use of methotrexate in patients with subcutaneous nodules, pulmonary disease, and NAFLD, use of rituximab in patients with hypogammaglobulinemia, and treatment of RA in patients with NTM lung disease. Areas covered in the 2015 guidelines that are not covered in this update include recommendations for patients with hepatitis C and solid malignancies. The panel did not vote on specific recommendations for patients with hepatitis C because curative antiviral therapy is now widely available. The panel did deliberate over PICO questions related to use of DMARDs in patients with solid malignancies. However, given the changing landscape of personalized treatments for many solid malignancies, the voting panel felt that a generalized recommendation was not possible.

On February 4, 2021, the FDA released a Drug Safety Alert noting a possible increased risk of major cardiovascular events and malignancies (excluding non-melanoma skin cancer) in patients with RA (over the age of 50 years with at least 1 risk factor for cardiovascular disease) participating in a randomized controlled trial designed to compare the safety of tofacitinib to adalimumab (18). Recommendations will be reviewed once peer-reviewed results are published. Rapidly evolving comparative effectiveness and safety signals associated with JAK inhibitors highlight the need to engage in a shared decision-making process when adjusting DMARDs (16,59). In addition, although previous recommendations cautioned against the use of TNF inhibitors in patients with skin cancer (1), the results of more recently published studies examining specific DMARD-related risks of non-melanoma skin cancer and melanoma do not support making a definite recommendation for or against specific DMARDs (60,61).

The panel also considered PICO questions related to current use of checkpoint inhibitor therapy, but the variability in current practice patterns and differences in treatment for specific cancer types precluded the development of specific recommendations for patients who are candidates for, or are currently receiving checkpoint inhibitor therapy. We anticipate that additional recommendations for patients with systemic rheumatic diseases and solid malignancies will be developed as further data become available. There were vigorous discussions pertaining to recommendations for specific DMARDs in patients with moderate-to-high disease activity despite csDMARDs and with a history of serious infection. However, the evidence was insufficient to support a recommendation. Future studies (using large registries and network meta-analyses) are needed to support specific recommendations for this patient population.

The recommendation statements in this update are not directly comparable to the ACR 2015 guidelines (1) because they do not retain the early versus established RA subgroups. Nevertheless, there are some notable differences. First, the 2015 guidelines recommend csDMARD monotherapy, preferably with methotrexate, for patients with both low and moderate/high disease activity, whereas this update recommends an initial trial of hydroxychloroquine or sulfasalazine for those with low disease activity. Second, the 2015 guidelines recommended DMARD tapering for patients who are in remission. In this update, tapering recommendations are made for patients who are in low disease activity or remission in the face of a paucity of data about when and how best to taper. The panel recommended that careful tapering might be considered if the patient wishes to cut back on their use of DMARDs. However, patients should be closely evaluated during any taper, and if a flare occurs, the prior regimen should be reinstituted promptly. Last, this update includes several recommendations *against* the use of glucocorticoid therapy. These recommendations were made in recognition of the frequent difficulty tapering glucocorticoids leading to undesirable prolonged use and the increasing evidence of the negative impact of glucocorticoids on long-term patient outcomes, including risk for infection, osteoporosis, and cardiovascular disease, in RA and other rheumatic diseases (62–65).

While consensus was easily reached on the majority of statements, 2 issues required prolonged discussion and debate. The decision on whether patients with an inadequate response to methotrexate should escalate to a bDMARD, tsDMARD, or triple therapy engendered much discussion with contrasting points of view. In the end, a recommendation was made in favor of a bDMARD or tsDMARD because of the more rapid onset of benefit and concerns related to the poor tolerability and durability of triple therapy in real-world practice (13,14). In particular, the patient panel highlighted the importance of a rapid onset of benefit after already having had an inadequate response to methotrexate. The conditional recommendation to initiate methotrexate therapy for patients with preexisting mild, stable lung disease was also rigorously debated. While minimizing the risk of toxicity is paramount, the voting panel favored a conditional recommendation to initiate methotrexate therapy in this clinical setting because of the vital role of this DMARD in the overall treatment of RA and lack of other comparable therapies without pulmonary risks.

Members of the voting panel agreed with the patient panel on the direction and strength of all but 2 recommendations. Patients were in favor of initial treatment with combination csDMARDs over methotrexate monotherapy because they placed greater value on the incremental benefits associated with combination therapy compared to clinicians. This preference was also stated in the 2015 guidelines (66). Patients also strongly preferred

discontinuing over a dose reduction of a DMARD whenever possible, whereas most clinicians on the voting panel preferred dose reduction. This discordance reflects patient preference to minimize use of medications once they reach target versus physician preference to minimize flare. However, both the patient and voting panel stressed the variability in patient preferences for tapering. These differences reinforce the importance of using a shared decision-making approach in RA.

When clinically relevant, recommendations specify the level of disease activity in the patient population (Table 1). However, evidence tables include pooled data from studies that often use different measures of disease activity; thus, specific definitions of low versus moderate-to-high disease activity are not provided for specific recommendations. Despite the large body of literature related to pharmacologic treatments for RA, the review team did not identify high-certainty evidence for many of the questions addressed. This discrepancy is due to the differences between clinically important PICO questions and the specific objectives of clinical trials. For example, few studies have examined how to best dose and administer methotrexate, the most effective and safe use of DMARDs in high-risk populations, and the risk–benefit tradeoffs associated with glucocorticoid use. Moreover, many trials could not be matched to specific PICO questions because of differences between the trials and the PICO questions' specified study populations and treatment comparisons. Thus, many recommendations are based largely on very low-certainty or low-certainty evidence. Incorporating medical evidence and expert input and consensus into clinical guidelines is core to the GRADE process and strengthens recommendations, particularly when there is limited evidence. Important gaps in knowledge are described in Table 7.

In summary, this update includes recommendations related to initiation and adjustment of DMARD therapy in patients with RA. It also emphasizes the importance of minimizing use of glucocorticoids. It is expected that additional data may modify the direction and/or strength of specific recommendations. The ACR will update the recommendations and answer these and other questions as new data are published.

ACKNOWLEDGMENTS

We thank Stanley B. Cohen, MD, for his contributions during the scoping phase of the project. We thank Cassandra Calabrese, DO, Leonard Calabrese, DO, Joseph Lim, MD, Danielle Antin-Ozerkis, MD, Marcus R. Pereira, MD, MPH, Jason E. Stout, MD, MHS, and Kevin Winthrop, MD, MPH, for their expert input as the voting panel considered recommendations related to comorbidities. We thank Nancy Baker, ScD, MPH, OTR/l, and Daniel White, PT, ScD, MSc, for their contributions during the scoping phase of the project, as well as their input during early deliberations by the voting panel. We thank the patients who (along with authors Kristine Carandang, PhD, OTR/L, and Shilpa Venkatachalam, PhD) participated in the patient panel meeting: Susan Campbell, Rachelle Crow-Hercher, MEd, Doug Davis, Sidney Harper, Faith Powell, Zenethia Roberts, Mary Turner, and C. Whitney White, PharmD. We thank the ACR staff, including Regina Parker for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, Robin Lane for assistance in manuscript preparation, and Jocelyn Givens for assistance with recruitment for the patient panel. We thank Janet Waters and Janet Joyce for their assistance in developing the literature search strategy, as well as performing the initial literature search and update searches.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Fraenkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Fraenkel, Bathon, England, St.Clair, Deane, Genovese, Kerr, Kremer, Sparks, Venkatachalam, Weinblatt, George, Johnson, Turner, Yaacoub, Akl.

Acquisition of data. Fraenkel, Bathon, England, St.Clair, Carandang, Deane, Genovese, Kerr, Kremer, J. Singh, Sparks, Al-Gibbawi, Baker, Barton, Cappelli, George, Johnson, Kahale, Karam, Khamis, Navarro-Millán, Mirza, Schwab, N. Singh, Turgunbaev, Turner, Yaacoub, Akl.

Analysis and interpretation of data. Fraenkel, Bathon, England, St.Clair, Arayssi, Deane, Genovese, Huston, Kerr, Kremer, Nakamura, Russell, J. Singh, Smith, Sparks, Venkatachalam, Weinblatt, Al-Gibbawi, Barbour, Barton, Chamseddine, Johnson, Kahale, Karam, Khamis, Navarro-Millán, Mirza, Schwab, N. Singh, Turgunbaev, Yaacoub, Akl.

ADDITIONAL DISCLOSURES

Author Genovese was employed by Stanford University Medical Center during development of this guideline but at the time of publication will also be employed by Gilead Sciences. Gilead Sciences had no financial or other interest in this project, had no input in the design, content, data collection, or analysis, and had no role in the writing or approval of this article.

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Arthritis & Rheumatology
Vol. 0, No. 0, Month 2022, pp 1–8
DOI 10.1002/art.42347
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American College of Rheumatology
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American College of Rheumatology/EULAR Remission Criteria for Rheumatoid Arthritis: 2022 Revision

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the EULAR Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

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Objective. In 2011, the American College of Rheumatology (ACR) and EULAR endorsed provisional criteria for remission in rheumatoid arthritis (RA), both Boolean- and index-based. Based on recent studies indicating that a higher threshold for the patient global assessment (PtGA) may improve agreement between the 2 sets of criteria, our goals were to externally validate a revision of the Boolean remission criteria using a higher PtGA threshold and to validate the provisionally endorsed index-based criteria.

Methods. We used data from 4 randomized trials comparing biologic disease-modifying antirheumatic drugs to methotrexate or placebo. We tested the higher proposed PtGA threshold of 2 cm (Boolean2.0) (range 0–10 cm) compared to the original threshold of 1 cm (Boolean1.0). We analyzed agreement between the Boolean- and index-based criteria (Simplified Disease Activity Index [SDAI] and Clinical Disease Activity Index [CDAI]) for remission and examined how well each remission definition predicted later good physical function (Health Assessment Questionnaire [HAQ] score ≤0.5) and radiographic nonprogression.

Results. Data from 2,048 trial participants, 1,101 with early RA and 947 with established RA, were included. The proportion of patients with disease in remission at 6 months after treatment initiation increased when using Boolean2.0 compared to Boolean1.0, from 14.8% to 20.6% in early RA and 4.2% to 6.0% in established RA. Agreement between Boolean2.0 and the SDAI or CDAI remission criteria was better than for Boolean1.0, particularly in early disease. Boolean2.0, SDAI, and CDAI remission criteria had similar positive likelihood ratios (LRs) to predict radiographic nonprogression and a HAQ score of ≤0.5 (positive LR 3.8–4.3). The omission of PtGA (BooleanX) worsened the prediction of good functional outcomes.

Conclusion. Using the Boolean 2.0 criteria classifies more patients as achieving remission and increases the agreement with index-based remission criteria without jeopardizing predictive value for radiographic or functional outcomes. This revised Boolean definition and the previously provisionally endorsed index-based criteria were endorsed by ACR and EULAR.

This article is published simultaneously in *Annals of the Rheumatic Diseases*.

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INTRODUCTION

Disease activity in rheumatoid arthritis (RA) was initially defined by a number of core set variables, agreed upon by the American College of Rheumatology (ACR) and EULAR in the 1990s (1,2). These variables comprised tender joint count (TJC) and swollen joint count (SJC), patient assessment of global disease activity (PtGA) and of pain, evaluator/physician global assessment (EGA), a measure of function such as the Health Assessment Questionnaire (HAQ), and an acute-phase reactant such as C-reactive protein (CRP) level.

At the time of defining the core set variables, remission was more aspirational than a realistic goal (3). Today, however, remission can be obtained in a sizable portion of patients and is seen as a major therapeutic target (4–6). A clinical definition of remission for RA should reflect no or only minimal disease activity, and patients attaining this state should have a low risk of both structural progression and functional impairment (6).

ACR and EULAR endorsed provisional remission criteria over 10 years ago (7). Their publication served the purpose of providing a common definition for this prime treatment target (8). Two types of remission definitions were agreed upon by the ACR/EULAR committee after extensive data analyses and consensus-based deliberations. The Boolean definition required that, to attain remission, each of 4 core set variables (TJC, SJC, PtGA, CRP) must have a value of ≤1. (PtGA is scored on a 0–10-point or 0–10-cm scale, CRP in mg/dl.) The index-based definition used the remission cutoff point of the simplified disease activity index (SDAI) (9). The committee also endorsed remission criteria that did not include CRP level, namely a Boolean definition that comprised SJC, TJC, and PtGA and an index definition based on the remission threshold of the clinical disease activity index (CDAI) (10).

Since their publication, arguments have been made claiming that remission definitions may, on the one hand, be too stringent, with the risk of overtreatment if used as treatment targets, or, on the other hand, too lenient, proposing addition of imaging confirmation of remission. A particular matter of debate was the requirement of achieving a PtGA score of ≤1; the stringent threshold for the PtGA has been criticized, because some patients do not achieve it despite the absence of tender and swollen joints and an elevated CRP level (11). Moreover, the agreement between the Boolean and index definitions was only moderate, primarily due to the PtGA threshold (12). However, the PtGA is the core set measure most sensitive to change in RA trials (1,13–15), best differentiating between patients receiving active treatment and those receiving placebo. Thus, PtGA is an important measure of disease activity. Consequently, the PtGA was included in the ACR core set, composite activity scores, and remission definitions. However, PtGA may also be influenced by other factors related to RA. For example, patients with pain from irreversible joint damage may have elevations in PtGA even if their RA is in clinical remission (16,17).

To circumvent the strictness of the 1.0 rule for PtGA and to increase the agreement with SDAI-defined remission, a higher PtGA threshold has been proposed (18,19). Furthermore, since the index-based criteria can be used instead of Boolean criteria, both criteria should identify the same patients as having disease in remission. However, remission rates based on SDAI are higher than those using the Boolean criteria, because summing several components permits 1 component, such as the PtGA, to be slightly elevated if compensated by a lower score in others (20). A study evaluating alternative Boolean definitions of remission, with PtGA thresholds ranging 1.0–2.5, found that using a threshold of 2 cm (Boolean2.0) led to a higher agreement with the index-based definition without jeopardizing the strong association between remission and subsequent good functional and radiographic outcomes, a key criterion in the development of the provisional definition of remission (12). The purpose of the present study is to externally validate the performance characteristics of this revision of the Boolean criteria (12) and provide external validation of the provisionally endorsed SDAI and CDAI remission definitions. This provides the evidence base for ACR and EULAR to fully endorse the remission criteria, changing their status from the current "provisional" to a "definite" status.

PATIENTS AND METHODS

Patients. RA patient data were retrieved from 4 clinical trials testing the efficacy of biologic disease-modifying antirheumatic drugs (bDMARDs) against placebo or placebo with methotrexate (MTX), with an available observation period between 1 and 2 years. The GO-AFTER trial tested golimumab as an active compound, the FUNCTION and LITHE trials tested tocilizumab, and the SERENE trial tested rituximab. GO-AFTER evaluated patients who were insufficient responders to TNF inhibitors (TNFi), LITHE and SERENE included patients with an insufficient response to MTX, and FUNCTION included MTX-naive patients with early RA. Results and detailed patient characteristics of the individual trials have been previously reported (21–24). These trials included RA patients with varying disease durations and treatment

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.42347&file=art42347-sup-0001-Disclosureform.pdf.

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Submitted for publication April 13, 2022; accepted in revised form September 2, 2022.

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histories. In all 4 trials, the PtGA was evaluated using a 100-mm visual analog scale (VAS).

Definitions of remission and their modifications. The Boolean definition includes SJC, TJC, PtGA (cm), and CRP levels (mg/dl); for a patient to meet remission criteria, all component scores must be ≤1 (in the case of a 100-mm VAS, this translates to a score of ≤10). A version without CRP was also approved by the ACR/EULAR committee (3-variable Boolean [3vBoolean]). The SDAI-based definition of remission sums the scores for the components used in the Boolean definition in addition to EGA, and patients meet criteria if the score is ≤3.3. The CDAI-based remission definition consists of the same components, excluding CRP level, and remission is fulfilled at a score of ≤2.8 (7).

Similar to a previous study (12), we increased the threshold of the PtGA criterion by steps of 0.5 cm from 1 cm up to 2.5 cm, and labeled these as Boolean1.0, Boolean1.5, Boolean2.0, and Boolean2.5. The Boolean definition that does not include the PtGA criterion was labeled as BooleanX; in this definition, only CRP, TJC, and SJC needed a score of ≤1 to attain remission, regardless of PtGA value (25).

Statistical analysis. We performed descriptive analyses and tested the revised Boolean2.0 criteria against the provisional Boolean1.0 criteria for convergent and predictive validity. Finally, we investigated the impact of the exclusion of the PtGA from the definition of remission (BooleanX). Analyses were performed on 6-month and 12-month data using SPSS Statistics 25 and Stata version 15. An experienced patient research partner (MW) was involved throughout the study. He took part in all meetings, reviewed data at different time points, and provided written as well as oral feedback. His contribution focused on a critical review of the PtGA as part of the RA definition of remission.

Descriptive analysis. We analyzed how the rates of remission at 6 and 12 months after treatment initiation in the trials were affected by the different modifications described above. For the Boolean modifications, we also studied which components prevented achievement of full remission by identifying participants who fulfilled 3 of 4 required criteria but not all 4 of them (11).

Convergent validity. We tested the agreement of different Boolean criteria with the index-based remission definitions. We cross-tabulated remission fulfilment for Boolean remission versions with the SDAI and CDAI definitions and analyzed their agreement using McNemar's test for agreement with kappa statistics. In addition, the well-established concordance between SDAI- and CDAI-defined remission was tested to confirm the interchangeability of these definitions.

We examined the optimal PtGA threshold to achieve concordance with SDAI-defined remission by carrying out classification and regression trees (CART) analyses (R rpart package; https://cran.r-project.org/web/packages/rpart/index.html), in which, after assuming that CRP, TJC, and SJC were all in remission (BooleanX), we asked what threshold of PtGA would provide the best prediction of SDAI-defined remission.

Predictive validity. As a next step, we explored the impact of using the modified Boolean- and index-based remission definitions assessed at 6 months after treatment initiation on outcomes at 1 year. Differences in mean radiographic progression (based on the change in modified total Sharp and van der Heijde score [mTSS] between baseline and 1 year) and the proportions of patients without progression (change in score ≤0) and with good function at 1 year (HAQ ≤0.5) were assessed. Attaining an HAQ of ≤0.5 without radiographic progression at 1 year of treatment was defined as a good combined outcome, similar to the procedure used to develop the provisional ACR/EULAR remission definition (7). These analyses were repeated separately for early and late RA participants. Positive and negative likelihood ratios (LRs) were calculated separately for each remission definition to assess predictive validity for good functional and structural outcomes.

Impact of PtGA score and PtGA exclusion from the remission definition. In addition to the comparison of Boolean2.0 to Boolean 1.0, we analyzed the effect of excluding PtGA from remission criteria (BooleanX) in the context of each of the above analyses.

RESULTS

Patients, remission rates, and components limiting achievement of remission. Data from 2,048 clinical trial participants, 1,101 with early RA (mean ± SD disease duration 0.8 ± 0.5 years) and 947 with established RA (mean ± SD disease duration 7.1 ± 5.4 years), were included. As expected, using Boolean2.0 yielded higher remission rates compared to Boolean1.0 at 6 months: 20.6% (n = 227) compared to 14.8% (n = 163) in early RA; 6.0% (n = 57) versus 4.2% (n = 40) in established RA (Figure 1). These correspond to a relative increase in remission rates of 39% and 42%, in early and established RA, respectively. This trend was consistent at 1 year, although remission rates were generally higher (Supplementary Figure 1, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42347). Omitting the PtGA criterion using the BooleanX definition further increased remission rates over Boolean2.0, in early RA (from 227 patients [20.6%] to 297 patients [27%]) and in established RA (from 57 patients [6%] to 95 patients [10%] patients at 6 months), with relative increases of 31% and 66%, respectively.

Within the total study population, 311 participants (15.2%) achieved "near misses" of Boolean remission, meaning that they fulfilled 3 of the 4 criteria. In 60% of these participants, this was due to not meeting the criterion of PtGA ≤1cm. By using Boolean2.0, this proportion was reduced to 47% of all near misses. Consequently, among all participants, 14% were classified as having Boolean2.0-defined remission, 5% missed achieving remission only because of the PtGA criterion, and 3% missed achieving

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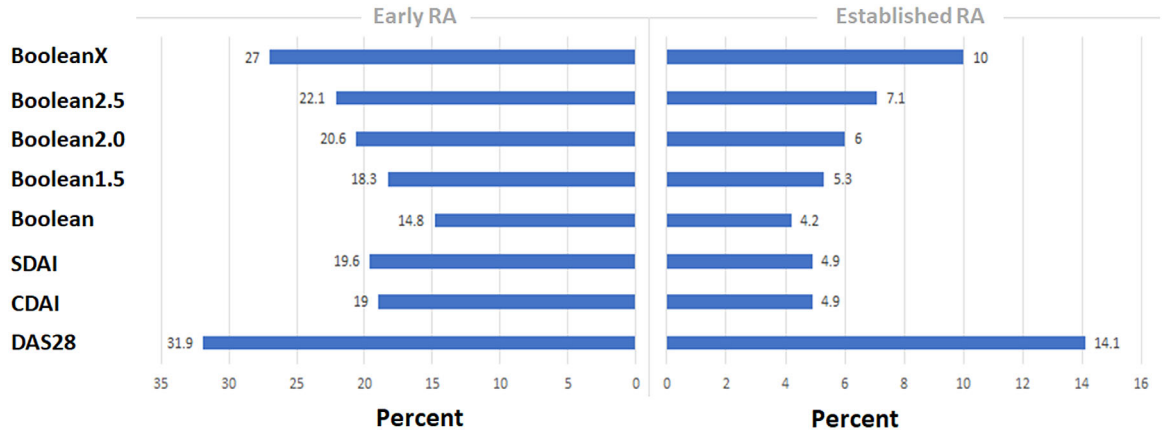

Figure 1. Rates of rheumatoid arthritis (RA) disease remission according to modified Boolean classifications, using a patient global assessment (PtGA) threshold of 1.0 ("Boolean"), 1.5, 2.0, 2.5, or omitting the PtGA completely (BooleanX), as well as according to the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and Disease Activity Score in 28 joints (DAS28) definitions. Rates at 6 months after treatment initiation are shown for patients with early RA and those with established RA.

remission only because of the SJC criterion (Supplementary Figure 2, https://onlinelibrary.wiley.com/doi/10.1002/art.42347).

Convergent validity. Increasing the PtGA cutoff from 1.0 to 2.0 cm for participants with early RA yielded higher concordance rates between Boolean- and SDAI-defined criteria for remission. This led to more participants contemporaneously fulfilling the SDAI and respective Boolean remission definition (increase from 71% to 92% of participants when using Boolean1.0 versus Boolean2.0) (Table 1). Rates of concordantly classified participants with respect to remission increased from 93.4% to 95.9% at 6 months. A similar increase in concordantly classified participants was observed for the agreement between the corresponding Boolean and CDAI definitions (Supplementary Table 1, https://onlinelibrary.wiley.com/doi/10.1002/art.42347). In patients with established RA, the percentage classified as having disease in remission by Boolean and CDAI or SDAI definitions likewise increased from 74% to 94% for SDAI and from 70% to 83% for CDAI, when using Boolean1.0 versus Boolean 2.0; and from 78% to 96% when using 3vBoolean1.0 versus 3vBoolean2.0 to assess agreement with CDAI. The proportion of participants concordantly classified as having disease in remission remained similar in established RA.

Kappa analyses showed higher agreement between SDAI-defined remission and Boolean2.0-defined than with Boolean1.0-defined remission at 6 months (Figure 2). The 12-month data showed similar results and are depicted in Supplementary Figure 3 (https://onlinelibrary.wiley.com/doi/10.1002/art.42347). Kappa estimates and 95% confidence intervals (95% CIs) of agreement with SDAI- and CDAI-defined remission at 6 months increased when using Boolean2.0 compared to Boolean1.0 definitions (0.86 [95% CI 0.83–0.89] versus 0.77 [95% CI 0.74–0.82] for SDAI at 6 months, and 0.81 [95% CI 0.77–0.84] versus 0.76 [95% CI 0.72–0.81] for CDAI at 6 months) (kappa

Table 1. Agreement rates between different modified Boolean remission definitions and the SDAI remission definition in RA patients at 6 months*

	Boolean1.0, no. in remission/ total no. (%)	Boolean2.0, no. in remission/ total no. (%)	BooleanX, no. in remission/ total no. (%)
Early RA			
Patients with disease in SDAI-based remission among those fulfilling Boolean remission definition	153/163 (93.9)	199/227 (87.7)	206/297 (69.4)
Patients with disease in Boolean-based remission among those fulfilling SDAI remission definition	153/216 (70.8)	199/216 (92.1)	206/216 (95.4)
Total concordantly classified	1,028/1,101 (93.4)	1,056/1,101 (95.9)	1,000/1,101 (90.8)
Established RA			
Patients with disease in SDAI-based remission among those fulfilling Boolean remission definition	34/40 (85)	43/57 (75.4)	45/95 (47.4)
Patients with disease in Boolean-based remission among those fulfilling SDAI remission definition	34/46 (73.9)	43/46 (93.5)	45/46 (97.8)
Total concordantly classified	929/947 (98)	930/947 (98.2)	896/947 (94.6)

* RA = rheumatoid arthritis; SDAI = Simplified Disease Activity Index.

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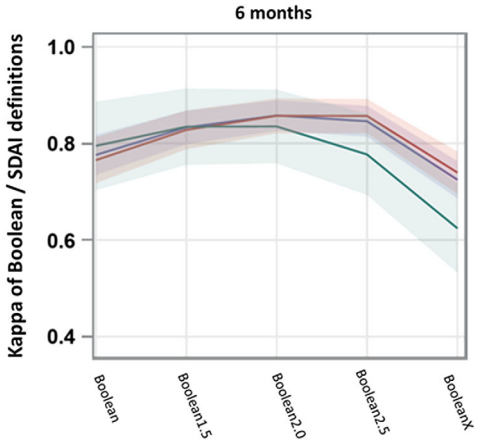

Kappa	All patients	Early RA	Established RA
Boolean	0.77 (0.74 – 0.82)	0.77 (0.72 – 0.81)	0.80 (0.70 – 0.89)
Boolean1.5	0.83 (0.79 – 0.87)	0.83 (0.79 – 0.87)	0.83 (0.76 – 0.91)
Boolean2.0	0.86 (0.83 – 0.89)	0.86 (0.82 – 0.89)	0.84 (0.75 – 0.91)
Boolean2.5	0.85 (0.81 – 0.87)	0.86 (0.82 - 0.89)	0.78 (0.70 – 0.90)
BooleanX	0.72 (0.69 - 0.76)	0.74 (0.69 – 0.78)	0.62 (0.53 – 0.72)

Figure 2. Kappa values and 95% confidence intervals (95% CIs) representing agreement between modified Boolean remission definitions and SDAI-defined remission, for patients with early RA (red line), those with established RA (green line), and all RA patients (blue line) at 6 months. Kappa estimates and 95% CIs are provided in the accompanying table. See Figure 1 for definitions.

curves for CDAI are shown in Supplementary Figure 4, https://onlinelibrary.wiley.com/doi/10.1002/art.42347).

A further increase in the PtGA threshold beyond 2 cm led to a decrease in concordance. Reduced concordance was particularly seen when omitting the PtGA (BooleanX) both in terms of percentage agreement and according to kappa estimates (Table 1 and Figure 2).

Additionally, CART analyses confirmed the percent agreement and kappa results: in participants with SJC, TJC, and CRP values of ≤1, and PtGA values of ≤2.3 cm at 6 months and ≤1.8 cm at 12 months showed the highest likelihood of concurrent SDAI-defined remission. The same analyses stratified by early or established RA yielded a PtGA threshold value of ≤2.3 cm in early RA and ≤1.4 cm in established RA at 6 months (≤1.5 cm in early RA and ≤1.9 cm in established RA at 12 months). Generally, all agreement estimates point to 2.0 cm as the optimal threshold.

Predictive validity. We studied rates of participants achieving a good functional outcome (HAQ ≤0.5) and no radiographic progression (ΔmTSS) at 1 year for participants classified by the different Boolean definitions at 6 months.

Similar results were found for Boolean2.0 and index-based definitions when predicting good functional outcome. HAQ scores at 12 months were as follows: mean ± SD 0.24 ± 0.40 for Boolean1.0, 0.31 ± 0.45 for Boolean2.0, 0.41 ± 0.53 for BooleanX, 0.27 ± 0.42 for SDAI, and 0.26 ± 0.42 for CDAI. Fewer participants scored an HAQ of ≤0.5 when the PtGA was omitted (70% in BooleanX versus 78% in Boolean2.0) (Table 2). Increasing the PtGA threshold for Boolean-based remission was associated with a linear increase in HAQ scores. While there was a drop in positive LR from 6.1 to 4.4 when using the Boolean2.0, this was similar to the positive LR predicting a good functional outcome for SDAI- and CDAI-based remission, which ranged from 4.3 to 4.9.

Table 2 outlines the similarity of LRs for predicting lack of radiographic progression during the first year when the different remission definitions were fulfilled at 6 months of treatment. The radiographic outcomes were similar regardless of the PtGA threshold or whether PtGA was included in the Boolean criteria, and scores were similar between different definitions (mean ± SD ΔmTSS 0.29 ± 2.08 for Boolean1.0, 0.25 ± 1.81 for Boolean2.0, 0.21 ± 1.9 for BooleanX, 0.27 ± 1.86 for SDAI, and 0.27 ± 1.9 for CDAI). This observation is consistent with previous findings that PtGA is not associated with radiographic

Table 2. Rates and LRs of RA patients achieving a good functional outcome (HAQ ≤0.5) and/or no radiographic progression (ΔmTSS) at 1 year, according to different remission criteria*

	HAQ ≤0.5				No increase in mTSS				Combined variables			
Criteria fulfilled	No	Yes	LR+ (range)	LR− (range)	No	Yes	LR+ (range)	LR− (range)	No	Yes	LR+ (range)	LR− (range)
Early RA												
Boolean1.0	43.3	85.9	6.19 (4.0–9.5)	0.78 (0.7–0.8)	65.6	78.5	1.76 (1.2–2.5)	0.92 (0.9–1.0)	31.7	67.5	3.54 (2.6–4.8)	0.79 (0.7–0.8)
Boolean2.0	41.5	80.6	4.23 (3.1–5.7)	0.72 (0.7–0.8)	64.4	79.3	1.85 (1.4–2.4)	0.87 (0.8–0.9)	29.6	65.2	3.19 (2.5–4.1)	0.72 (0.7–0.8)
BooleanX	40.5	74.1	2.76 (2.3–3.3)	0.58 (0.5–0.7)	63.1	79.5	1.86 (1.4–2.4)	0.82 (0.8–0.9)	28.4	60.3	2.59 (2.1–3.2)	0.67 (0.6–0.7)
SDAI	41.4	83.3	3.88 (3.1–4.9)	0.61 (0.5–0.7)	64.6	79.2	1.83 (1.2–2.5)	0.88 (0.8–0.9)	29.7	66.7	3.41 (2.6–4.4)	0.72 (0.7–0.8)
CDAI	41.6	83.7	4.25 (3.4–5.4)	0.60 (0.5–0.7)	64.8	78.9	1.81 (1.3–2.5)	0.89 (0.8–0.9)	29.9	67	3.46 (2.7–4.5)	0.73 (0.7–0.8)
Established RA												
Boolean1.0	29.2	72.5	5.86 (3.0–11.6)	0.92 (0.9–1.0)	32.6	37.5	1.23 (0.7–2.3)	0.99 (0.9–1.0)	12.1	22.5	2.02 (1.0–4.1)	0.96 (0.9–1.0)
Boolean2.0	28.7	68.4	4.19 (2.5–7.0)	0.85 (0.8–0.9)	32.4	40.4	1.38 (0.8–2.3)	0.98 (0.9–1.0)	11.8	24.6	2.27 (1.3–4.0)	0.93 (0.9–1.0)
BooleanX	28.1	57.9	2.42 (1.6–3.8)	0.86 (0.8–1.0)	31.3	46.3	1.76 (1.2–2.6)	0.93 (0.9–1.0)	11.6	21.1	1.86 (1.2–2.9)	0.91 (0.8–1.0)
SDAI	29	71.7	4.84 (2.7–8.5)	0.86 (0.8–0.9)	32.6	37	1.2 (0.7–2.1)	0.99 (0.9–1.0)	12	23.9	2.19 (1.1–4.2)	0.95 (0.9–1.0)
CDAI	28.7	76.1	4.84 (2.7–8.5)	0.86 (0.8–0.9)	32.6	37	1.2 (0.7–2.1)	0.99 (0.9–1.0)	11.8	28.3	2.74 (1.5–5.1)	0.93 (0.9–1.0)

* Positive likelihood ratios (LR+) and negative LRs (LR−) for reaching the respective outcome at 12 months if remission is achieved at 6 months are shown. RA = rheumatoid arthritis; HAQ = Health Assessment Questionnaire; ΔmTSS = change in modified Sharp/van der Heijde score; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index.

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progression (12,26). Using the different Boolean definitions as well as index-based definitions led to similar proportions of participants with disease in remission who had radiographic progression (defined as ΔmTSS>0) during the first year (29.6% for Boolean1.0, 28.5% for Boolean2.0, 28.6% for BooleanX, 28.2% for SDAI, and 28.6% for CDAI).

The proportion of participants achieving both good radiographic and functional outcomes were similar for all remission definitions, from 57% to 60% (58.6% for Boolean1.0, 57.3% for Boolean 2.0, 59.2% for SDAI, and 60.4% for CDAI), except for BooleanX (50.8%). Again, index-based remission definitions performed similarly to Boolean1.0 and Boolean2.0 definitions with respect to their predictive ability (positive LR between 3.8 and 4.3). This pattern could also be seen when analyzing data on early RA and established RA, separately (Table 2). However, good functional outcomes when using BooleanX were even less frequent in established RA compared to early RA (HAQ ≤0.5 in established RA was 57% compared to 74% in early RA). Of note, no differences in radiographic progression in patients with established RA were observed between the remission definitions fulfilled. Overall, more than two-thirds of patients with established RA showed radiographic progression throughout the first year.

DISCUSSION

This study provides evidence of external validation of the previously proposed modification of the Boolean ACR/EULAR remission criteria, to include a threshold of 2 cm rather than 1 cm for the PtGA criterion, and of the provisionally endorsed index-based remission definitions. The study was performed using independent clinical trial data sets not included in any of the previous studies (e.g., the data sets generating the provisional definition of remission and the recent analyses on raising the PtGA threshold [7,12] in which the revised threshold was derived). Our study assessed different aspects of validity for the revised definition of remission. The composition of this patient population was heterogenous in terms of disease duration and previous DMARD treatments, and our results are therefore applicable to a broad spectrum of patients with RA (21–24).

The remission validation outlined here builds on work done 10 years ago when the selection of components was undertaken by a large ACR/EULAR consortium (7). Due to criticism around the stringently low threshold of the PtGA component within the Boolean remission definition (11,25,27) and concerns that the 2 approaches (Boolean-based versus index-based) to remission were not concordant, alternative thresholds for the PtGA were explored using multiple clinical trial data sets (12). Our analyses support the notion of a slight increase of the PtGA threshold since it provides better agreement with the SDAI remission definition and higher rates of Boolean-defined remission, without jeopardizing the prediction of good long-term functional and radiographic outcomes.

Our results replicate previous findings that a Boolean definition using 2 cm as threshold for PtGA (Boolean2.0) yields better agreement with both index-based remission definitions than Boolean1.0 (12). Furthermore, patients who attain Boolean2.0, CDAI, and SDAI remission thresholds at 6 months have a higher likelihood of good functional and radiographic outcomes after 12 months of treatment than those attaining Boolean-based disease remission without PtGA (BooleanX). We have also shown the agreement between the 3-variable Boolean approach definition and the CDAI definition, which can be applied during a clinic visit, without knowledge of current acute-phase reactant levels.

The PtGA threshold within the remission criteria does not influence the prediction of radiographic nonprogression, as all tested definitions yielded the same positive LRs for nonprogression of ~1.7 and the same proportions of patients not progressing (~79%). This is consistent with findings from a recent meta-analyses including data from 11 clinical trials showing that people fulfilling the SJC, TJC, and CRP criteria but not the PtGA criterion demonstrate better radiographic outcomes than those not in any Boolean remission category (26). We note that successful management of RA is not only defined by the prevention of joint damage, but, ideally, attaining remission should also prevent residual symptoms that matter to patients, such as pain, fatigue, and anxiety.

The PtGA has not only been criticized for its stringent threshold in the remission definition. The Outcome Measures in Rheumatology (OMERACT) Working Group focusing on "Remission in RA: Patient Perspective" questioned whether the PtGA is the best instrument to reflect the perspective of patients in the current Boolean remission definition. They explored the effect of replacing PtGA with 3 patient-assessed domains identified by patients as most important: pain, fatigue, and independence. Their search for a better incorporation of the patient perspective has not yet resulted in a promising set of validated patient-reported outcome measures that can replace the PtGA. In their most recent working group report, they concluded that there is currently insufficient evidence to propose a change to the existing ACR/EULAR remission criteria (28). This report also discussed the concept of a "dual-target" approach, trying to decouple the assessment of disease activity from disease impact in defining remission (25,29). At this stage no data are available about the effectiveness and feasibility of such a dual-target approach.

Concerns have been expressed that the ACR/EULAR remission criteria allow few patients to achieve disease remission. Within our validation work, we additionally provide data on the shift in remission frequencies and the distribution of patients that miss Boolean-defined remission due to fulfilling only 3 of 4 criteria. By using a threshold of 2 cm rather than 1 cm in the revised Boolean definition, 40% more participants in our data sets achieved disease remission (14% instead of 10%). Importantly, when applying the Boolean2.0 definition, the SJC criterion threshold of 1 seems to be nearly as prominent in limiting participants

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attaining full remission as the PtGA criterion (3% due to high SJC and 5% to high PtGA when fulfilling the other 3 criteria). The revised PtGA threshold of 2 cm has been proposed as 1 item in a set of 7 criteria that defined minimal disease activity of RA by OMERACT in 2005 (30). Notably, the definition of remission should remain strict and ensure beneficial long-term outcomes for patients with RA and prevent unnecessary treatment escalation at the same time. Furthermore, it appears that changes in the overall approach to treating RA before patients enter clinical trials or trends over time have led to much higher provisional ACR/EULAR remission rates in more recent clinical trials than in earlier ones, with recent rates reaching ~30% in early disease, 20% in patients with insufficient response to MTX, and 15–20% in patients with insufficient response to bDMARDs (31–35).

A preferable approach for more patients to achieve remission is to foster a collaborative relationship between patients and clinicians, to initiate treatment early, and to utilize a treat-to-target approach (8), rather than omitting potentially problematic items such as the PtGA (36,37). Studies have shown that a treat-to-target approach is not yet fully implemented in clinical practice; in one-third of instances where treatment was not increased, this was influenced by factors unrelated to RA and in another third it was the patient's preference to continue receiving the current treatment (38,39). All measurements and their interpretations need, in any case, to be complemented by the discussion between the patient and rheumatology clinician to reflect and decide on the appropriate steps in a shared decision (40,41).

Remission has become a key target for the management of patients with RA (42). The ACR/EULAR 2011 initiative on remission criteria was undertaken to harmonize the definition of the term "remission" and thus to facilitate the fair assessment and comparison of remission rates in clinical trials and clinical practice (e.g., for different health care settings or providers). It will be helpful to further study the performance of the revised criteria in trials using other antirheumatic drugs, such as JAK inhibitors, and in other countries and ethnic groups, since RA severity and the interpretation of the PtGA may vary across ethnicities. We validated the results of the performance of the Boolean2.0 and the provisionally endorsed index-based remission definitions. With the validation of the threshold of 2 cm for the PtGA, we propose that these revised ACR/EULAR remission criteria be adopted both for future clinical trials and as a target in clinical practice.

ACKNOWLEDGMENTS

We would like to thank the companies that kindly provided the patient-level data from their trials (Hoffmann-La Roche, Janssen Biotech).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Studenic had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Studenic, Aletaha, Lacaille, Smolen, Felson.

Acquisition of data. Studenic, Aletaha.

Analysis and interpretation of data. Studenic, Aletaha, de Wit, Stamm, Alasti, Lacaille.

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2022 American College of Rheumatology (ACR) Guideline for Exercise, Rehabilitation, Diet, and Additional Integrative Interventions for Rheumatoid Arthritis

Guideline Summary

Revised January 13, 2023

This American College of Rheumatology (ACR) guideline addresses the use of exercise, rehabilitation, diet, and additional integrative interventions in conjunction with disease-modifying anti-rheumatic drugs (DMARDs) as part of an integrative management approach for people with rheumatoid arthritis (RA).

An interprofessional guideline development group developed clinically relevant Population, Intervention, Comparator, and Outcome (PICO) questions. A literature review team then completed a systematic literature review and applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the certainty of evidence. An interprofessional Voting Panel (n=20 participants) that included three persons with RA achieved consensus on the direction and strength of recommendations. These teams included individuals with expertise in epidemiology, exercise physiology, GRADE methodology, integrative medicine, nursing, nutrition, occupational therapy, physical therapy, rheumatology, and social work. Guiding principles through the guideline development process specified that integrative interventions considered in this guideline should complement pharmacologic treatments, highlighted an interprofessional approach for the management of RA, and emphasized that shared decision-making is needed when caring for people with RA.

The Voting Panel achieved consensus on one strong recommendation for exercise and conditional recommendations pertaining to exercise type, rehabilitation interventions, diet interventions, and additional integrative interventions (**Table 1**). **These recommendations are specific to RA management,** understanding that other medical indications and general health benefits may exist for many of these interventions.

This guideline provides initial ACR recommendations on integrative interventions for the management of RA to accompany DMARD treatments. The broad range of interventions included in these recommendations illustrates the importance of an interprofessional team-based approach to RA management. The conditional nature of most recommendations requires clinicians to engage patients in shared decision-making when applying these recommendations.

Table 1. Recommendations on integrative interventions for the management of rheumatoid arthritis (RA)

Exercise	Rehabilitation	Diet	Additional
Consistent engagement in exercise (++)	Comprehensive occupational therapy (+)	Mediterranean-style diet (+)	Standardized self-management program (+)
Aerobic exercise (+)	Comprehensive physical therapy (+)	Against formally defined diet other than Mediterranean-style (-)	Cognitive behavioral therapy and/or mind-body approaches (+)
Aquatic exercise (+)	Hand therapy exercises (+)	Against dietary supplements (-)	Acupuncture (+)
Resistance exercise (+)	Splinting, orthoses, compression, bracing, and/or taping (+)		Massage therapy (+)
Mind-body exercise (+)	Joint protection techniques (+)		Thermal modalities (+)
	Activity pacing, activity modification, energy conservation, and/or fatigue management (+)		Against electrotherapy (-)
	Assistive devices, adaptive equipment, and/or environmental adaptations (+)		Against chiropractic therapy (-)
	Vocational rehabilitation, work site evaluations and/or modifications (+)		

Strong recommendations **for** an intervention are shown in dark green and ++.
Conditional recommendations **for** an intervention are shown in light green and +.
Conditional recommendations **against** an intervention are shown in light red and -.

This summary was approved by the ACR Board of Directors on October 31, 2022. These recommendations are included in a full manuscript, which will be submitted for publication in Arthritis & Rheumatology and Arthritis Care and Research.

Revised January 13, 2023 – Activity pacing recommendation added from prior version

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Revised January 13, 2023 – Activity pacing recommendation added from prior version

Diagnosis and differential diagnosis of rheumatoid arthritis

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Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Jan 2023. | **This topic last updated:** May 28, 2022.

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INTRODUCTION

Rheumatoid arthritis (RA) is a symmetric, inflammatory, peripheral polyarthritis of unknown etiology. It typically leads to deformity through the stretching of tendons and ligaments and destruction of joints through the erosion of cartilage and bone. If it is untreated or unresponsive to therapy, inflammation and joint destruction lead to loss of physical function, inability to carry out daily tasks of living, and difficulties in maintaining employment. Uncontrolled inflammation may have other health risks including higher rates of cardiovascular disease, osteoporosis, and certain types of cancer (eg, lymphoma).

Early recognition and treatment with disease-modifying antirheumatic drugs (DMARDs) is important in achieving control of disease and prevention of joint injury and disability. However, in patients with early disease, the joint manifestations are often difficult to distinguish from other forms of inflammatory polyarthritis. The more distinctive signs of RA, such as joint erosions, rheumatoid nodules, and other extraarticular manifestations, are seen primarily in patients with longstanding, poorly controlled disease but are frequently absent on initial presentation.

This topic will review the approach to the diagnosis and differential diagnosis of RA. The clinical features of this disorder, its extraarticular manifestations, and laboratory markers that are clinically useful in the diagnosis of RA are discussed in detail separately. (See "Clinical manifestations of rheumatoid arthritis" and "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis" and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis".)

EVALUATION FOR SUSPECTED RA

Rheumatoid arthritis (RA) should be suspected in the adult patient who presents with inflammatory polyarthritis. The initial evaluation of such patients requires a careful history and physical examination, along with selected laboratory testing to identify features that are characteristic of RA or that suggest an alternative diagnosis. (See "Clinical manifestations of rheumatoid arthritis" and 'Differential diagnosis' below.)

We focus especially on the following for the purposes of diagnosis:

- We perform a thorough medical history, with particular attention to joint pain, reported swelling, and the presence, location (peripheral joints rather than low back), and duration (at least 30 minutes) of morning stiffness. The absence of other conditions or symptoms suggesting an alternative diagnosis, such as psoriasis, inflammatory bowel disease (IBD), or a systemic rheumatic disease such as systemic lupus erythematosus (SLE), helps to exclude other disorders.

  Symptoms of arthritis that have been present for a short time (eg, less than six weeks) may well be due to an acute viral polyarthritis rather than to RA. The longer symptoms persist, the more likely the diagnosis of RA becomes. Thus, in patients presenting very early, close observation with frequent follow-up appointments is required, with repeated evaluations for joint swelling and elevations in acute phase reactants, before establishing a formal diagnosis.

  In a minority of patients, several such visits are required before the diagnosis of RA is established. (See "Clinical manifestations of rheumatoid arthritis", section on 'Typical 'classic' RA' and 'Differential diagnosis' below.)

- A complete physical examination is indicated to assess for synovitis, including the presence and distribution of swollen or tender joints and limited joint motion; extraarticular disease manifestations, such as rheumatoid nodules; and signs of diseases, such as SLE or psoriasis, included in the differential diagnosis. (See "Clinical manifestations of rheumatoid arthritis", section on 'Symptoms and physical findings' and "Rheumatoid nodules" and 'Differential diagnosis' below.)

- We perform the following laboratory tests, which support the diagnosis if positive and/or elevated:

  - Rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) – We perform both RF and ACPA testing when initially evaluating a patient with suspected RA. The results of both tests are informative, since a positive result for either test increases overall diagnostic sensitivity, while the specificity is increased

when both tests are positive. Despite this, both tests are negative on presentation in up to 50 percent of patients and remain negative during follow-up in 20 percent of patients with RA.

For most patients, serologic evidence of disease will be present by the time symptoms are noted. However, where the diagnosis is uncertain, repeating a serologic analysis for ACPAs and RF 6 to 12 months after the initial evaluation can identify individuals who develop serologic evidence to support the diagnosis. Once the diagnosis of RA is established, evidence does not support serial testing of these serologies for disease prognosis [1]. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Rheumatoid factors' and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)

- Erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) – Both the ESR and CRP are typically elevated in RA. These may also be repeated subsequent to the initial evaluation and diagnosis for assessment and monitoring of systemic inflammation, as indicated, over the course of disease. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Erythrocyte sedimentation rate' and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'C-reactive protein'.)

- We perform the following testing in all patients, which may be helpful in the differential diagnosis of RA and as baseline testing for monitoring of disease activity or progression and medication safety:

  - Antinuclear antibody (ANA) testing – A negative ANA helps exclude SLE and other systemic rheumatic diseases; the ANA may be positive in up to one-third of patients with RA. In patients with a positive ANA, anti-double stranded deoxyribonucleic acid (DNA) and anti-Smith antibody testing should also be performed; these antibodies have higher specificity for SLE. (See "Measurement and clinical significance of antinuclear antibodies".)

  - Complete blood count (CBC) with differential and platelet count, tests of liver and kidney function, serum uric acid, and a urinalysis – The CBC is often abnormal in RA, with anemia and thrombocytosis consistent with chronic inflammation. Liver and kidney testing abnormalities could indicate a disorder other than RA; if caused by comorbid conditions, they may affect therapeutic choices or drug dosing. Hyperuricemia may prompt additional efforts, including arthrocentesis and crystal search, to exclude gout; polyarticular gout can infrequently be mistaken for RA. (See 'Differential diagnosis' below and "Hematologic complications of rheumatoid

arthritis", section on 'Anemia' and "Hematologic complications of rheumatoid arthritis", section on 'High or low platelet count'.)

- Radiographs of the hands, wrists, and feet – We obtain radiographs during the initial evaluation primarily as a baseline for monitoring disease progression. However, characteristic joint erosions may be observed in patients presenting with symptoms for the first time and, hence, aid in diagnosis and prognosis. Additionally, in patients with other disorders, such as psoriatic arthritis, spondyloarthropathy, gout, or chondrocalcinosis, radiographic changes more characteristic of these conditions may point to an alternative diagnosis. (See '2010 ACR/EULAR criteria' below and 'Differential diagnosis' below and "Clinical manifestations of rheumatoid arthritis", section on 'Imaging'.)

- We perform the following studies in selected patients:

  - Serologic studies for infection – In patients with a very short duration of symptoms (less than six weeks) particularly those who are seronegative for ACPA and RF, we perform serologic testing for human parvovirus B19, hepatitis B virus (HBV), and hepatitis C virus (HCV). In areas endemic for Lyme disease, we perform serologic studies for Borrelia as well. In people who live in or have traveled to parts of the world where mosquito (*Aedes aegypti* and *Aedes albopictus)*-bite transmitted viral diseases are prevalent, chikungunya virus infection should be suspected in patients with fever and arthralgia, as this may be followed by a chronic polyarthritis; diagnosis is confirmed by serologic tests. Other mosquito-borne illnesses such as Zika or dengue may be considered in the appropriate clinical context. (See 'Viral polyarthritis' below and "Viruses that cause arthritis" and "Diagnosis of Lyme disease" and "Chikungunya fever: Epidemiology, clinical manifestations, and diagnosis".)

  - Synovial fluid analysis – We perform arthrocentesis and synovial fluid analysis for the diagnosis or exclusion of gout, pseudogout, or an infectious arthritis if a joint effusion is present and if there is uncertainty regarding the diagnosis, particularly in the setting a monoarthritis, oligoarthritis, or asymmetric joint inflammation. Synovial fluid testing should include a cell count and differential, crystal search, and Gram stain and culture. (See "Clinical manifestations of rheumatoid arthritis", section on 'Laboratory findings' and "Synovial fluid analysis".)

  - Magnetic resonance imaging (MRI) and ultrasound – MRI studies and ultrasonography do not have an established role in the routine evaluation of patients with polyarthritis. However, MRI and ultrasound are more sensitive than radiography at detecting changes resulting from synovitis and may be helpful in establishing the presence of synovitis in patients with normal radiographs and

uncertainty regarding either the diagnosis or the presence of inflammatory changes, such as patients with obesity or subtle findings on examination. Abnormalities such as synovitis, osteitis, and erosion observed on imaging studies should be considered consistent with, but not diagnostic of, RA as each can be observed in other conditions. (See "Clinical manifestations of rheumatoid arthritis", section on 'Imaging'.)

DIAGNOSIS

Our diagnostic criteria — The diagnosis of rheumatoid arthritis (RA) can be made when the following clinical features are all present:

- Inflammatory arthritis involving three or more joints. (See "Clinical manifestations of rheumatoid arthritis", section on 'Symptoms and physical findings'.)
- Positive rheumatoid factor (RF) and/or anti-citrullinated peptide/protein antibody (ACPA), such as anti-cyclic citrullinated peptide antibody (anti-CCP) testing. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)
- Elevated levels of C-reactive protein (CRP) or the erythrocyte sedimentation rate (ESR). (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Erythrocyte sedimentation rate'.)
- Diseases with similar clinical features have been excluded, particularly psoriatic arthritis, acute viral polyarthritis, polyarticular gout or calcium pyrophosphate deposition disease, and systemic lupus erythematosus (SLE). (See 'Differential diagnosis' below.)
- The duration of symptoms is more than six weeks.

These criteria are consistent with the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR; formerly known as European League Against Rheumatism) classification criteria for RA (see '2010 ACR/EULAR criteria' below). A higher titer of RF or ACPA and a greater number of swollen joints each increases the probability of RA.

The diagnosis of RA may also be made in some patients who do not meet all of our criteria (eg, patients negative for RF and ACPA). (See 'Patients not meeting above criteria' below.)

Inflammatory arthritis — Arthritis is typically present in the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the hands. The wrists are also commonly

involved, as are the second to fifth metatarsophalangeal (MTP) joints in the feet, but any upper or lower extremity joint may be affected. Symmetric polyarthritis, particularly of the MCP, MTP, and/or PIP joints, strongly suggests RA. Although distal interphalangeal (DIP) joint disease can occur in patients with RA, DIP involvement strongly suggests a diagnosis of osteoarthritis or psoriatic arthritis. (See "Clinical manifestations of rheumatoid arthritis", section on 'Symptoms and physical findings' and 'Osteoarthritis' below and 'Psoriatic arthritis' below.)

Serology — RFs occur in 70 to 80 percent of patients with RA. Their diagnostic utility is limited by their relatively poor specificity, since they are found in 5 to 10 percent of healthy individuals, 20 to 30 percent of people with SLE, virtually all patients with mixed cryoglobulinemia (usually caused by hepatitis C virus [HCV] infections), and in those with many other inflammatory conditions. The prevalence of RF positivity in healthy individuals rises with age. Higher titers of RF (at least three times the upper limit of normal) have somewhat greater specificity for RA. Low titer RF levels are thus commonly observed and should be interpreted with caution if the clinical context is not otherwise consistent with RA. (See "Rheumatoid factor: Biology and utility of measurement" and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Rheumatoid factors'.)

Antibodies to citrullinated peptides/proteins are usually measured by enzyme-linked immunosorbent assays (ELISAs) using citrullinated proteins as antigen. ACPAs have a similar sensitivity to RF for RA but have a higher specificity (95 to 98 percent) [2-5]. The specificity is greater in patients with higher titers of ACPAs (at least three times the upper limit of normal). Another test, anti-mutated citrullinated vimentin, gives similar results to ACPA and is used as an alternative in some laboratories [6]. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)

Acute phase reactants — Elevations of the ESR and/or CRP level are consistent with the presence of an inflammatory state, such as RA. Normal acute phase reactants may occur in untreated patients with RA, but such findings are infrequent and should prompt consideration of alternative diagnoses [7]. The degree of elevation of these acute phase reactants varies with the severity of inflammation and synovitis. As an example, an ESR of 50 to 80 is not uncommon in patients with severely active RA. By comparison, an ESR of 20 to 30 can be observed with only a few mildly to moderately active joints. Although increased levels of acute phase reactants are not specific for RA, they are often useful for distinguishing inflammatory conditions from noninflammatory disorders that present with musculoskeletal symptoms (eg, osteoarthritis or fibromyalgia). (See "Acute phase reactants" and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Erythrocyte sedimentation rate' and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'C-reactive protein'.)

Patients not meeting above criteria — The diagnosis of RA may also be made in patients without all the criteria described in the previous section. Examples include the following:

- **Seronegative RA** – Patients who lack both RF and ACPAs may be diagnosed with RA based upon findings otherwise characteristic of RA if appropriate exclusions have been met. The presence of a large number of swollen joints in a symmetric, small joint pattern or the presence of features such as erosion or rheumatoid nodules provides greater confidence in a diagnosis of RA in the absence of positive serologic testing. Such patients with seronegative RA differ from ACPA-positive patients genetically and in their environmental risks, disease severity, and clinical responsiveness to some medications [8]. Additional research is needed to better characterize this population. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis".)

- **Recent onset RA** – To avoid delays in initiation of treatment for patients with a severe disease presentation, patients with disease for less than six weeks may be diagnosed with RA based upon findings otherwise characteristic of RA, including ACPAs, if testing for viral serologies is negative, and if other appropriate exclusions have been met. (See 'Evaluation for suspected RA' above and 'Viral polyarthritis' below.)

- **Inactive RA** – Patients without active arthritis or elevated acute phase reactants (eg, due to treatment of recent onset disease or with longstanding disease) may be diagnosed with RA based upon well-documented past findings characteristic of RA, especially in the presence of positive testing for RF and ACPA, or typical bone erosions on radiography, and in the absence of an alternative more likely diagnosis.

Patients in the several categories above, and other patients who should be diagnosed with RA but do not meet our standard criteria, will generally have findings that are consistent with the 2010 ACR/EULAR classification criteria for RA [9,10]. These criteria were developed for the classification of patients with RA for the purpose of epidemiologic studies and clinical trials, not primarily for clinical diagnosis. Nevertheless, the same features that are of value in classification tend to be useful for the purpose of diagnosis in clinical practice. Further study is required to establish their utility as diagnostic criteria in general practice. (See 'Classification criteria' below.)

CLASSIFICATION CRITERIA

The 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria focus on features that would identify patients at an earlier stage of disease than would the previously used criteria that had been last revised in 1987 [9-12]. The 1987 ACR criteria were formulated to distinguish patients with

established rheumatoid arthritis (RA) from patients with other defined rheumatic diseases; the 2010 ACR/EULAR criteria for RA focused on identifying the factors, among patients newly presenting with undifferentiated inflammatory synovitis, which could allow for the identification of patients for whom the risk of symptom persistence or structural damage is sufficient to be considered for intervention with disease-modifying antirheumatic drugs (DMARDs) [9,10]. (See '2010 ACR/EULAR criteria' below and '1987 ACR criteria' below.)

2010 ACR/EULAR criteria — Using the 2010 ACR/EULAR classification criteria for RA, classification as definite RA is based upon the presence of synovitis in at least one joint, the absence of an alternative diagnosis that better explains the synovitis, and the achievement of a total score of at least 6 (of a possible 10) from the individual scores in four domains [9,10,13]. The highest score achieved in a given domain is used for this calculation. These domains and their values are:

- Number and site of involved joints
  - 2 to 10 large joints (from among shoulders, elbows, hips, knees, and ankles) = 1 point
  - 1 to 3 small joints (from among the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists) = 2 points
  - 4 to 10 small joints = 3 points
  - Greater than 10 joints (including at least 1 small joint) = 5 points
- Serological abnormality (rheumatoid factor or anti-citrullinated peptide/protein antibody)
  - Low positive (above the upper limit of normal [ULN]) = 2 points
  - High positive (greater than three times the ULN) = 3 points
- Elevated acute phase response (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) above the ULN = 1 point
- Symptom duration at least six weeks = 1 point

In addition to those with the criteria above, which are best suited to patients with newly presenting disease, the following patients are classified as having RA:

- Patients with erosive disease typical of RA with a history compatible with prior fulfillment of the criteria above

- Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who have previously fulfilled the criteria above based upon retrospectively available data

1987 ACR criteria — It is important to recognize that RA was defined in virtually all clinical trials of drugs for RA initiated from 1987 through 2010 based upon the criteria developed and validated by the ACR (previously the American Rheumatism Association) in 1987 (table 1) [11,12]. A patient was classified as having RA if at least four of these seven criteria were satisfied; four of the criteria must have been present for at least six weeks: morning stiffness, arthritis of three or more joint areas, arthritis of the hands, and symmetric arthritis. Rheumatoid factor (RF) was included as a criterion, but anti-citrullinated peptide antibody (ACPA) testing was not available at that time. The other two criteria were rheumatoid nodules and radiographic erosive changes typical of RA, but these are generally not present in the early stages of disease.

Thus, while these criteria were very good at separating inflammatory from noninflammatory arthritis, the major drawback of the 1987 criteria has been their insensitivity in identifying some patients with early disease who subsequently develop typical established RA [12]. The criteria also did not require any exclusions, and patients could initially fulfill the diagnostic criteria but occasionally evolve into other diagnoses, particularly systemic lupus erythematosus (SLE), Sjögren's syndrome, scleroderma, mixed connective tissue disease, psoriatic arthritis, and crystalline arthritis.

DIFFERENTIAL DIAGNOSIS

Joint pain involving the hands is a common clinical presentation for a variety of conditions, thus a number of other diagnoses must be considered in the differential diagnosis of rheumatoid arthritis (RA). The evaluation of patients with polyarticular pain is described in detail separately (see "Evaluation of the adult with polyarticular pain"), and the features of disorders that are included in the differential diagnosis of RA are described below.

Viral polyarthritis — A number of viral infections may cause an acute viral polyarthritis.

- Viral infections such as rubella [14], parvovirus B19 [15], and hepatitis B virus (HBV) can cause an acute polyarthritis syndrome that may be mistaken for the inflammatory polyarthritis of RA. However, the syndrome is usually short-lived, lasting only from a few days to several weeks, and rarely beyond six weeks. Hepatitis C virus (HCV) can cause a polyarthritis or oligoarthritis in a minority of patients, but is more commonly associated with arthralgias.

Serologic testing can help identify patients with HBV, HCV, or human parvovirus B19 in some individuals with early disease, but a viral etiology cannot always be excluded until after symptoms are present for at least six to eight weeks in the absence of diagnostic serologic testing for a specific virus (see "Viruses that cause arthritis") Unlike rheumatoid factor (RF) (which may occur in patients with a variety of infections, including HCV infection), anti-citrullinated peptide antibodies (ACPAs) are usually negative in patients with HCV infection who do not have RA. For mild disease presentations, conservative approaches to management may be reasonable for symptoms lasting less than six weeks. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)

- Increasingly reported in travelers, alphaviruses are globally distributed mosquito-borne ribonucleic acid (RNA) viruses that cause epidemics of polyarthritis/arthralgia [16,17]. Among all of the viruses that can cause arthritis, the alphaviruses are unusual because nearly all symptomatic infections in adults result in joint symptoms. The incubation period lasts from several days to three weeks; infection is typically associated with triad of fever, arthritis, and rash [16]. However, all aspects of the triad may not be present, thereby making the diagnosis difficult.

  One such alphavirus, Chikungunya, has become a global disease with increasing world travel and has caused large outbreaks in Italy, India, Indian Ocean islands, and in the Caribbean region and surrounding countries [18,19]. Patients with more persistent disease can mimic seronegative RA clinically to a sufficient degree to satisfy the 2010 classification criteria for RA if the initial symptoms of fever and rash and history of travel to an endemic region are not appreciated [20]. Serologic studies can help to document exposure to the Chikungunya virus. (See "Chikungunya fever: Epidemiology, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)

  Alphavirus infections generally resolve over three to six months. The diagnosis of alphavirus infection can be made by appropriate serologic testing in travelers from endemic areas with persistent arthritic symptoms. (See "Viruses that cause arthritis", section on 'Alphaviruses' and "Chikungunya fever: Epidemiology, clinical manifestations, and diagnosis".)

- A large joint arthritis has been reported in association with human T lymphotropic virus type 1 (HTLV-I) [21]. These infections are sometimes associated with the presence of RFs (usually in low titer), antinuclear antibodies (ANA), and elevated acute phase reactants. HTLV-I infections can generally be distinguished from RA by the

finding of specific antiviral antibodies and the typically self-limited nature of arthritis associated with HTLV-I. Testing may be considered in endemic areas.

Other systemic rheumatic diseases — Early RA may be difficult to distinguish from the arthritis of systemic lupus erythematosus (SLE), Sjögren's syndrome, dermatomyositis (DM) and antisynthetase syndrome, and overlap syndromes such as mixed connective tissue disease. RF can also often be elevated in other systemic rheumatic diseases, most notably Sjögren's syndrome. In contrast with RA, these disorders are generally characterized by the presence of other systemic features, such as rashes, dry mouth and dry eyes, myositis, or nephritis, and by various autoantibodies not often seen in RA.

While diagnostic uncertainty in early RA is expected, the diagnosis should become clearer with time.

Taken together, the pattern of longstanding disease, morning stiffness, symmetric arthritis, subcutaneous nodules, and the deformities characteristic of RA does not develop in these other disorders. There are several exceptions to this observation:

- Morning stiffness is common in all inflammatory arthritides. Symmetric arthritis is seen in patients with SLE and can be present in other disorders. Infrequently, nodules similar to those seen in RA may occur in patients with SLE, and other nodular lesions may mimic rheumatoid nodules. (See "Rheumatoid nodules", section on 'Differential diagnosis'.)

- An erosive arthritis has been described in some overlap syndromes, particularly those associated with anti-tRNA synthetases and anti-U1 RNP antibodies [22]. (See "Clinical manifestations and diagnosis of mixed connective tissue disease".)

- Jaccoud's arthropathy occurs in up to 5 to 10 percent of patients with Sjögren's syndrome or SLE and can also occur in sarcoidosis [23]. (See "Arthritis and other musculoskeletal manifestations of systemic lupus erythematosus" and "Sarcoid arthropathy".)

  The joint deformities of Jaccoud's arthropathy are not caused by destruction of joints but by loosening and lengthening of periarticular structures and tendons. The ulnar drift or swan neck deformities caused by this disorder resemble RA superficially but can be distinguished by the fact that they are "correctable" on physical examination: fingers with these deformities can be moved manually back into normal alignment. In addition, radiographs in Jaccoud's arthropathy rarely reveal the cartilage loss, erosions, or cysts that are typical of longstanding RA.

Palindromic rheumatism — The term palindromic rheumatism refers to episodes of joint inflammation sequentially affecting one to several joint areas for hours to days, with

symptom-free periods that may last from days to months. Some patients presenting with this syndrome eventually develop a well-defined rheumatic disease, the most common being RA (ranging from 28 to 67 percent); some of the remaining patients develop SLE and other systemic disorders [24,25]. Patients with ACPAs appear more likely to progress to definite RA [26,27]. Close follow-up and specific serologic evaluation can help distinguish among these disorders. (See "Clinical manifestations of rheumatoid arthritis", section on 'Palindromic rheumatism'.)

Osteoarthritis — Osteoarthritis (OA) can be confused with RA in the middle aged or older patient when the small joints of the hands are involved. However, different patterns of clinical involvement usually permit the correct diagnosis (table 2). The following are examples (see "Clinical manifestations and diagnosis of osteoarthritis"):

- OA of the fingers typically affects the distal interphalangeal joints and is frequently associated with Heberden's nodes in this area. In contrast, RA typically affects the MCP and proximal interphalangeal (PIP) joints and is not associated with Heberden's nodes.
- The carpometacarpal joint of the thumb is typically involved in OA.
- Swelling of the joints is hard and bony in OA. In contrast, soft, warm, boggy, and tender joints are typical of RA.
- Stiffness of the joint is a very common feature of RA but is relatively uncommon in OA. Furthermore, the stiffness of RA is characteristically worse after resting the joint (eg, morning stiffness), while the stiffness of OA, if present, is typically worse after any effort and is often described as evening stiffness. Morning stiffness in OA, when present, is usually transient or lasts no more than a few minutes, unlike the more sustained stiffness typical of RA.
- Radiographs also help distinguish RA from OA. OA is characterized by narrowing of the joint space due to cartilage loss and osteophytes due to bone remodeling, but not erosions or cysts.
- OA is classically associated with the absence of RFs and normal levels of acute phase reactants. However, RFs may be present, usually in low titer, consistent with the patient's (older) age.
- Erosive or inflammatory osteoarthritis can cause severe and rapidly progressive arthritis in the small joints of the hands, often at middle age. Swelling in the PIPs with central joint erosion may be present. Central erosions (found in the center of the joint space) should be distinguished from the marginal erosions of RA, which are found at the margin of the joint space. Distinction from RA can be made by characteristic

findings on radiographs as well as a lack of systemic inflammation and serologic markers.

Stenosing tenosynovitis — Tendon pathology in the hand is common among patients with diabetes, thyroid disease, or occupational risk factors, and can resemble the hand pain and tenosynovitis seen in some patients with RA. Narrowing of flexor tendon sheaths may cause triggering, or locking, of the digits and refer pain to the fingers, particularly during activity (see "Trigger finger (stenosing flexor tenosynovitis)"). Hand pain may be present even in the absence of overt triggering. Diabetic cheiroarthropathy is a related condition that results in difficulty in the extension of the digits of the hand. Tendon pathology may be distinguished from RA by eliciting pain over the flexor tendons at the base of the digit and by the absence of synovitis in the joints of the hand. (See "Limited joint mobility in diabetes mellitus".)

Carpal tunnel syndrome — Hand and wrist pain may be a symptom of RA, and synovitis in the wrist from RA may also cause median nerve entrapment and the presence of classic symptoms of carpal tunnel syndrome. Thus, the presence of carpal tunnel syndrome does not exclude concurrent RA. However, carpal tunnel syndrome is common and observed at higher rates in patients with some comorbid conditions (eg, diabetes). A sensation of hand swelling along with burning and numbness, often experienced at night or in the morning, are common symptoms of median nerve entrapment. Carpal tunnel syndrome should be considered in patients who demonstrate a positive Tinel or Phalen sign, have thenar wasting, and/or demonstrate poor hand dexterity or weakness in the "pinch test." (See "Carpal tunnel syndrome: Clinical manifestations and diagnosis".)

Reactive arthritis and arthritis of inflammatory bowel disease — Reactive arthritis often presents as a monoarthritis or oligoarthritis in large joints, such as the knees, and RA may occasionally present in this fashion as well [28]. The physical signs of both reactive arthritis and RA can be identical in the knees. (See "Reactive arthritis".)

The following findings on history, physical examination, or other assessments are more consistent with reactive arthritis than RA:

- History of recent urethritis or enteric infection
- Asymmetric pattern of joint involvement
- Symptoms or signs of enthesopathy (inflammation at the site where a tendon inserts into a bone, eg, the insertion point of the Achilles tendon into the heel)
- Keratoderma blennorrhagica or circinate balanitis (see "Reactive arthritis" and "Reactive arthritis", section on 'Extraarticular signs and symptoms')
- Radiologic evidence of sacroiliitis and/or spondylitis
- The presence of human leukocyte antigen (HLA)-B27

Involvement of the hands in reactive arthritis does not pose as great a diagnostic dilemma as that of the knees. Hand arthritis is more commonly asymmetric than in RA. Furthermore, reactive arthritis will often involve not only the joint but also the tenosynovium, entheses, and surrounding tissues of the digit, giving rise to a characteristic "sausage" swelling of the fingers (or toes if the feet are involved) (picture 1).

The arthritis associated with inflammatory bowel disease (IBD) or other gastrointestinal (GI) disorders is also part of the differential diagnosis. While IBD-related arthritis is more commonly a large-joint oligoarticular arthritis or spondyloarthritis with sacroiliitis, patients with IBD may infrequently develop a peripheral polyarthritis with prominent involvement of the metacarpophalangeal (MCP) joints that can be mistaken for RA. This disorder may be missed if abdominal symptoms or symptoms of diarrhea and/or blood or mucus in the stool are not prominent or are not specifically sought in the history. (See "Clinical manifestations and diagnosis of arthritis associated with inflammatory bowel disease and other gastrointestinal diseases".)

Psoriatic arthritis — Psoriatic arthritis can be difficult to distinguish from RA because a symmetric polyarthritis can be observed in both disorders [29]. We generally make the diagnosis of psoriatic arthritis in such patients who also have psoriasis and are seronegative for RF and ACPA. However, we diagnose RA in those with a symmetric polyarthritis who are seropositive for at least one of these antibodies, since skin psoriasis is so common. However, serologic testing and skin findings may not be informative, since patients with RA may not have RF or ACPA (eg, seronegative RA) and the joint symptoms of psoriatic arthritis may precede the onset of skin disease by many years. Such patients should be evaluated and monitored for other signs more characteristic of psoriatic arthritis, such as nail changes or enthesitis; occasional patients exhibit overlapping features of both disorders. Since management at this stage is highly similar between these disorders, distinguishing the two entities is not necessary in order to initiate therapy.

In some patients with a symmetric inflammatory polyarthritis, the only clue to the diagnosis of psoriatic arthritis is a family history of psoriasis. However, in the majority, the findings of skin psoriasis, nail changes (onychodystrophy), sausage toes or fingers, oligoarticular asymmetric large joint or spinal involvement, and/or arthritis mutilans help distinguish the two entities. (See "Clinical manifestations and diagnosis of psoriatic arthritis".)

Polymyalgia rheumatica — Polymyalgia rheumatica (PMR) can sometimes be mistaken for RA in patients presenting with more limited arthritis over the age of 50 who are seronegative or have a low RF titer. Unlike RA, PMR is usually associated with marked myalgias in the shoulders and hips, and joint involvement tends to be milder, more limited, and more often asymmetric.

Stiffness is thus more axial in PMR and more likely to be described as difficulty getting out of bed, while stiffness in the small joints of the hands and other involved joints predominates in RA, in which difficulty buttoning clothing is more likely to be reported. However, similar complaints to RA may be present in patients with PMR with synovitis affecting the small joints in the hands.

The arthritis in PMR tends to respond strikingly to modest doses of glucocorticoids used to control other symptoms [30]. In patients initially diagnosed with PMR, persistent or recurrent small joint arthritis with tapering of glucocorticoids and the absence of other findings suggestive of PMR may lead to a change in the diagnosis to RA after several months or even years of treatment. (See "Clinical manifestations and diagnosis of polymyalgia rheumatica".)

Crystalline arthritis — Crystalline arthritis (gout and acute or chronic calcium pyrophosphate deposition disease [CPPD; pseudogout]) can become chronic and even assume a polyarticular distribution. The diagnosis is established by the finding of urate or calcium pyrophosphate crystals, respectively, in synovial fluids. The presence of tophi on physical examination, the lack of detection of serologic markers of RA, and the characteristic appearance of gouty erosions are also useful in distinguishing RA from polyarticular gout. Chondrocalcinosis on radiographs may be helpful in distinguishing CPPD from RA. Since crystalline arthritis is not uncommon, its presence does not exclude the diagnosis of RA. (See "Clinical manifestations and diagnosis of gout" and "Clinical manifestations and diagnosis of calcium pyrophosphate crystal deposition (CPPD) disease".)

Bacterial infectious arthritis

Lyme arthritis — Lyme arthritis, a late manifestation of Lyme disease, occurs primarily in individuals who live in or travel to Lyme disease-endemic areas. Lyme arthritis is characterized by intermittent or persistent inflammatory arthritis in a few large joints, most typically monoarthritis of the knee. The most commonly involved joints, after the knee, are the shoulder, ankle, elbow, temporomandibular joint, and wrist. Migratory arthralgias without frank arthritis may occur during early localized or early disseminated Lyme disease. (See "Musculoskeletal manifestations of Lyme disease".)

The diagnosis of Lyme arthritis can usually be made by serologic testing, which should be performed in patients presenting with undiagnosed inflammatory arthritis in endemic areas. In addition, several clinical features help distinguish Lyme arthritis from RA. Involvement of the small joints of the hands and feet is uncommon in patients with Lyme arthritis. Furthermore, many, but not all, patients with Lyme arthritis will describe an antecedent history of erythema migrans or other early disease manifestations. (See "Musculoskeletal manifestations of Lyme disease", section on 'Diagnosis of Lyme arthritis'.)

Other infectious arthritis — Infectious arthritis is usually monoarticular, but polyarthritis can occur. The diagnosis is established by culturing the pathogen from the synovial fluid or from the blood. Patients with septic arthritis may or may not appear toxic on examination, depending upon the stage of their infection, the presence of medications that can mask infection (eg, glucocorticoids), and other clinical variables. Peripheral blood leukocytosis with a left shift is common but not invariably present.

A low threshold for suspecting infection is required, particularly in compromised hosts. Patients with RA are at increased risk for joint infections because a damaged joint can serve as a nidus of infection. Synovial fluid changes, including marked granulocytosis and low glucose levels, are similar to those seen in RA. (See "Septic arthritis in adults".)

Hypermobility syndrome and fibromyalgia — Pain, rather than stiffness or swelling, is the dominant symptom of the two common disorders, hypermobility syndrome (which includes hypermobility spectrum disorder and hypermobility type Ehlers-Danlos syndrome) and fibromyalgia [31,32]. Although the hypermobility syndromes and fibromyalgia can both bear superficial resemblances to RA due to the presence of polyarthralgia, there are important distinguishing features:

- The hypermobility syndromes are associated with hyperextensible joints, and patients lack signs of synovitis. (See "Clinical manifestations and diagnosis of hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorder".)
- Fibromyalgia is associated with tender points at nonarticular sites and chronic widespread pain. However, there is no evidence of synovitis, such as swelling, warmth, or diminished joint range of motion, although patients may exhibit joint line tenderness on exam. (See "Clinical manifestations and diagnosis of fibromyalgia in adults".)
- Neither the hypermobility syndromes nor fibromyalgia are associated with significant titers of RF or ACPAs or with elevated levels of acute phase reactants.

Although RA is usually not difficult to distinguish from fibromyalgia, diagnostic confusion can arise when assessment of serologies or acute phase reactants is performed and modestly elevated results are observed that are of unclear significance. In addition, a significant minority of patients with RA also develop fibromyalgia. The source of complaints in such patients needs to be carefully assessed to distinguish heightened pain sensitivity from pain related to inflammatory joint disease.

Paraneoplastic and cancer treatment-related disease — Joint pain or frank polyarthritis can occur in association with cancer. The following are some examples:

- **Hypertrophic osteoarthropathy** – Patients with hypertrophic osteoarthropathy, sometimes termed hypertrophic pulmonary osteoarthropathy, typically demonstrate clubbing of the digits, joint pain, and periosteal new bone formation. Additionally, they give a characteristic history suggestive of bone pain and often describe the pain as deep and achy; nocturnal pain is common. Joint effusions may occur. (See "Malignancy and rheumatic disorders", section on 'Hypertrophic osteoarthropathy'.)

- **Myelodysplasia** – Patients with myelodysplastic syndrome sometimes develop an inflammatory polyarthritis that mimics RA [33]. The majority of patients are seronegative for RF and few are positive for anti-citrullinated peptide antibody or exhibit erosive changes on joint radiography. The arthritis may precede the diagnosis of myelodysplasia in at least half of the patients. In a cohort study of 87 patients with myelodysplastic syndrome, five (6 percent) had inflammatory arthritis that resembled RA [34]. Persistence of anemia, other cytopenias, or elevated acute phase reactants despite control of the arthritis should heighten suspicion of myelodysplasia [33]. (See "Clinical manifestations and diagnosis of myelodysplastic syndromes (MDS)".)

- **Immune checkpoint inhibitor therapy** – Cancer therapy that involves use of immune checkpoint inhibitor (ICI) immunotherapy may result in a number of rheumatologic and other adverse effects, including inflammatory arthritis that resembles RA. The joint symptoms may range from mild to severe and can develop at almost any time during ICI therapy. RF and ACPAs are often absent. (See "Rheumatologic complications of checkpoint inhibitor immunotherapy", section on 'Inflammatory arthritis'.)

Multicentric reticulohistiocytosis — Multicentric reticulohistiocytosis is a rare but highly destructive form of arthritis [35,36]. The rapid joint destruction of multicentric reticulohistiocytosis resembles the arthritis mutilans occasionally observed in RA. Multiple smooth, shiny, erythematous nodules located in the periungual region suggest multicentric reticulohistiocytosis. Binucleated or multinucleated foreign body type giant cells are present on skin or synovial biopsies in multicentric reticulohistiocytosis [37,38]. In a minority of patients, an underlying malignancy may be present. (See "Cutaneous manifestations of internal malignancy", section on 'Multicentric reticulohistiocytosis'.)

Multicentric reticulohistiocytosis is relatively resistant to glucocorticoids and to disease-modifying antirheumatic drugs (DMARDs) [35,36,39-42].

Sarcoid arthropathy — Chronic arthritis in sarcoidosis may be oligoarticular or polyarticular and can appear similar to RA in some patients. It most frequently affects the ankles, knees, hands, wrist, and MCP and PIP joints, and it is frequently associated with parenchymal pulmonary disease. (See "Sarcoid arthropathy".)

This disorder is distinguished from RA by the following findings:

- Elevated serum concentrations of angiotensin-converting enzyme (ACE) are found in up to 50 percent of patients.
- A chest radiograph may reveal characteristic findings of sarcoidosis.
- The pattern of acute arthritis with Lofgren's syndrome in patients with sarcoidosis is not observed in those with RA.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Rheumatoid arthritis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Rheumatoid arthritis (The Basics)")
- Beyond the Basics topics (see "Patient education: Rheumatoid arthritis symptoms and diagnosis (Beyond the Basics)" and "Patient education: Rheumatoid arthritis treatment (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Evaluation in patients suspected of RA** – Rheumatoid arthritis (RA) should be suspected in the adult patient who presents with inflammatory polyarthritis. The initial evaluation of such patients requires a careful history and physical examination,

along with selected laboratory testing to identify features that are characteristic of RA or that suggest an alternative diagnosis. (See 'Evaluation for suspected RA' above and 'Differential diagnosis' above.)

- **Components of the medical evaluation** – The following components of the medical evaluation are helpful in making a clinical diagnosis of RA, both for the identification of characteristic findings and for the exclusion of other diagnoses (see 'Evaluation for suspected RA' above):
  - **History** – A thorough medical history, with particular attention to joint pain, stiffness, and associated functional difficulties.
  - **Physical examination** – A complete physical examination to assess for synovitis, limited joint motion, extraarticular disease manifestations, and signs of diseases included in differential diagnosis.
  - **Laboratory testing** – Basic and selected laboratory testing, including assays for acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPAs), and antinuclear antibodies (ANA).
  - **Imaging** – Selected imaging studies, including bilateral radiographs of the hands, wrists, and feet.
  - **Role of arthrocentesis** – Arthrocentesis, if there is diagnostic uncertainty, to establish the presence of an inflammatory process within the joint and rule out other causes (eg, infection, crystal arthritis).
- **Diagnosis in patients with characteristic findings** – The diagnosis of RA can be made in a patient with inflammatory arthritis involving three or more joints, positive RF and/or anti-citrullinated peptide/protein antibody, disease duration of more than six weeks, and elevated CRP or ESR, but without evidence of alternative diagnoses with similar clinical features. (See 'Our diagnostic criteria' above.)
- **Diagnosis in patients without all of the classic findings** – RA may also be diagnosed in patients without all of the classic findings of disease. This includes patients with seronegative RA, those with clinically quiescent disease, and those with recent onset RA. Such patients have findings/clinical features that are generally consistent with those described as meeting the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for RA. (See 'Patients not meeting above criteria' above.)

- **Classification criteria** – The 2010 ACR/EULAR classification criteria for RA were developed primarily for the identification for research purposes of patients with RA who are at high risk of persistent symptoms and joint injury unless treated with disease-modifying antirheumatic drugs (DMARDs). These criteria have replaced the 1987 criteria, which were based only upon patients with established disease. (See 'Classification criteria' above.)

- **Differential diagnosis** – The differential diagnosis of RA includes multiple disorders that can generally be distinguished by history, physical examination, and limited laboratory and radiographic testing, based upon evidence of the following features (see 'Differential diagnosis' above):

  - Evidence of osteoarthritis (table 2), carpal tunnel syndrome, or tendinopathy (suggesting a noninflammatory process)

  - Limited duration of symptoms (eg, in viral arthropathy)

  - The presence of other diseases (eg, in psoriatic arthritis or arthritis of inflammatory bowel disease [IBD])

  - The pattern of joint involvement and other symptoms (eg, in psoriatic arthritis, spondyloarthropathy, or polymyalgia rheumatica [PMR])

  - The presence of systemic features (eg, in systemic lupus erythematosus [SLE], sarcoidosis, or dermatomyositis [DM])

  - Diagnostic laboratory tests associated with other conditions (eg, specific autoantibodies in SLE, synovial fluid crystals in gout or calcium pyrophosphate disease)

  - Relatively high specificity of ACPAs for RA

ACKNOWLEDGMENTS

The UpToDate editorial staff acknowledges Ravinder N Maini, BA, MB BChir, FRCP, FMedSci, FRS and PJW Venables, MA, MB BChir, MD, FRCP, who contributed to earlier versions of this topic review.

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Topic 7504 Version 29.0

Arthritis Care & Research
Vol. 64, No. 5, May 2012, pp 640–647
DOI 10.1002/acr.21649
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SPECIAL ARTICLE

Rheumatoid Arthritis Disease Activity Measures: American College of Rheumatology Recommendations for Use in Clinical Practice

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.

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Objective. **Although the systematic measurement of disease activity facilitates clinical decision making in rheumatoid arthritis (RA), no recommendations currently exist on which measures should be applied in clinical practice in the US. The American College of Rheumatology (ACR) convened a Working Group (WG) to comprehensively evaluate the validity, feasibility, and acceptability of available RA disease activity measures and derive recommendations for their use in clinical practice.**

Methods. **The Rheumatoid Arthritis Clinical Disease Activity Measures Working Group conducted a systematic review of the literature to identify RA disease activity measures. Using exclusion criteria, input from an Expert Advisory Panel (EAP), and psychometric analysis, a list of potential measures was created. A survey was administered to rheumatologists soliciting input. The WG used these survey results in conjunction with the psychometric analyses to derive final recommendations.**

Results. **Systematic review of the literature resulted in identification of 63 RA disease activity measures. Application of exclusion criteria and ratings by the EAP narrowed the list to 14 measures for further evaluation. Practicing rheumatologists rated 9 of these 14 measures as most useful and feasible. From these 9 measures, the WG selected 6 with the best psychometric properties for inclusion in the final set of ACR-recommended RA disease activity measures.**

Conclusion. **We recommend the Clinical Disease Activity Index, Disease Activity Score with 28-joint counts (erythrocyte sedimentation rate or C-reactive protein), Patient Activity Scale (PAS), PAS-II, Routine Assessment of Patient Index Data with 3 measures, and Simplified Disease Activity Index because they are accurate reflections of disease activity; are sensitive to change; discriminate well between low, moderate, and high disease activity states; have remission criteria; and are feasible to perform in clinical settings.**

Introduction

The last 2 decades have witnessed a dramatic improvement in the treatment of rheumatoid arthritis (RA), with disease remission now considered a realistic goal for many patients (1). Surrogate measures of outcome such as disease activity measures can facilitate clinical decision mak-

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Significance & Innovations

- This study systematically examines published measures of disease activity in rheumatoid arthritis (RA), identifying those measures that are valid and feasible to perform in clinical settings.
- Incorporation of these validated RA disease activity measures into a practice's workflow will facilitate adherence to the American College of Rheumatology guidelines for the treatment of RA and provide the necessary tools for treating to target.
- Routine use of these measures will allow clinicians to demonstrate that they are providing high-quality care for RA, as measured by nationally endorsed quality measures.

ing to achieve these goals, and studies in RA show that treating to a target improves outcomes (2–4). As health care reform in the US accelerates efforts to improve quality, assessment of disease activity in RA has become a nationally endorsed quality measure. For example, the Physician Quality Reporting System, a pay-for-reporting program administered by the Centers for Medicare and Medicaid Services, includes a quality measure assessing whether physicians measure RA disease activity using a standardized scale or composite index and classify RA disease activity as low, moderate, or high at least yearly (5).

Despite the push from various stakeholders in the health care system to standardized disease activity assessment in RA and growing evidence that treating to target is effective, most US rheumatologists do not routinely use standardized measures in clinical practice. The myriad available instruments and lack of formal recommendations on which measures are best suited for different practice settings likely contribute to this lack of implementation. As a first and important step in addressing this issue, the American College of Rheumatology (ACR) commissioned a Working Group (WG) to use a validated multistep process to derive recommendations for the use of RA disease activity measures in clinical practice.

The goal of this effort was to determine which disease activity measures reliably distinguish between different levels of disease activity in RA and are feasible to implement in clinical practice. In this article, we review the methods for arriving at our recommendations, summarize the important components of the selected measures, and also discuss some of the practical issues that rheumatologists should consider in deciding which measure to implement in their practice setting.

Dr. Anderson owns stock and/or stock options in Abbot Laboratories. Dr. Michaud has received consultant fees, speaking fees, and/or honoraria (less than $10,000) from the Mayo Foundation. Dr. Saag has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Amgen, AstraZeneca, Lilly, Genentech, Merck, Horizon, Sanofi-Aventis, Novartis, and Pfizer. Dr. Kazi has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Genentech and Centocor.

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Submitted for publication October 23, 2011; accepted in revised form February 14, 2012.

Materials and Methods

The methods used to derive our recommendations are summarized very briefly here, but are outlined in significantly greater detail in Supplementary Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Figure 1 shows an overview of the methodology used, which included a combination of a systematic literature review, psychometric analyses, validated group methods, and physician surveys.

First, the WG conducted a systematic literature review to identify available RA disease activity measurement tools and applied initial exclusion criteria (see Supplementary Figure 1 and Supplementary Table 1, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Next, an RA disease activity measurement Expert Advisory Panel (EAP), consisting of rheumatologists with published expertise in RA disease activity measurement, was consulted to review measures meeting criteria for inclusion. The EAP ranked the recommended measures by using the Outcome Measures in Rheumatology filter on truth, discrimination, and feasibility (6). The WG then further condensed the number of measures based on a detailed review of the psychometric properties of each measure. The abbreviated measure set was then incorporated into a survey administered to practicing rheumatologists to gather information regarding usefulness, feasibility, and willingness to use in daily clinical practice. Collation of the information gathered in these steps formed the basis for the final WG recommendations.

Results

Systematic literature review and EAP ratings. Sixty-three tools to measure RA disease activity were initially identified, 16 of which met prespecified exclusion criteria (see Supplementary Figure 1 and Supplementary Table 1, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). From the remaining 47 measures, 4 were combined into 2 measures. Forty-five measures were then presented to members of the EAP, and ratings of familiarity with the measure, personal experience using the measure, and a final recommendation regarding use in clinical practice resulted in selection of 31 measures (see Supplementary Table 2, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Qualitative feedback from the EAP was then used to further abbreviate this list of measures, including recommendations to exclude instruments that primarily measure quality of life (n = 10), do not indicate the current state of

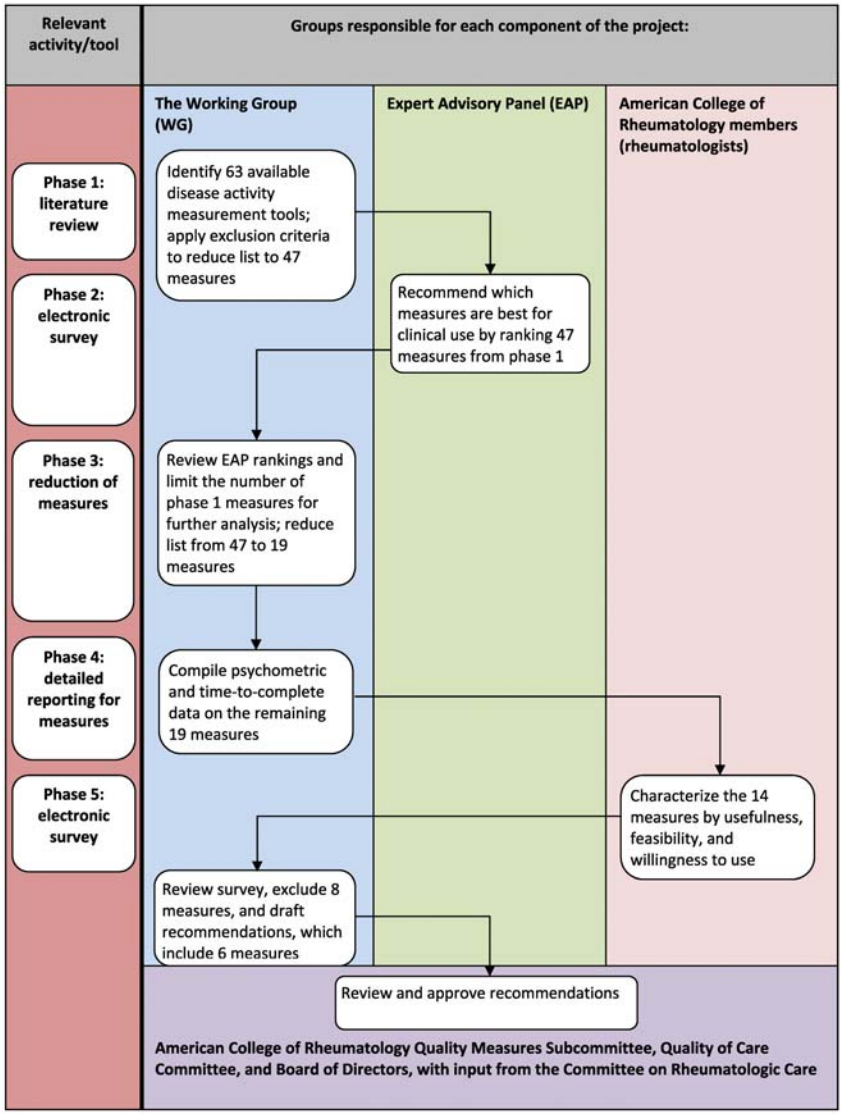
Relevant activity/tool
Groups responsible for each component of the project:
The Working Group (WG)
Expert Advisory Panel (EAP)
American College of Rheumatology members (rheumatologists)
Phase 1: literature review
Identify 63 available disease activity measurement tools; apply exclusion criteria to reduce list to 47 measures
Phase 2: electronic survey
Recommend which measures are best for clinical use by ranking 47 measures from phase 1
Phase 3: reduction of measures
Review EAP rankings and limit the number of phase 1 measures for further analysis; reduce list from 47 to 19 measures
Phase 4: detailed reporting for measures
Compile psychometric and time-to-complete data on the remaining 19 measures
Phase 5: electronic survey
Characterize the 14 measures by usefulness, feasibility, and willingness to use
Review survey, exclude 8 measures, and draft recommendations, which include 6 measures
Review and approve recommendations
American College of Rheumatology Quality Measures Subcommittee, Quality of Care Committee, and Board of Directors, with input from the Committee on Rheumatologic Care

Figure 1. Flow diagram of methods.

disease activity (i.e., require the calculation of change scores [n = 2]), are confined to a single body region (n = 1), or are antiquated and no longer in current use (n = 1).

Psychometric analyses. The remaining 19 measures were then subjected to a detailed review of psychometric properties, including evaluation of their reliability, validity, and responsiveness. Five measures were excluded in this phase based on the lack of defined remission and/or disease activity criteria. The psychometric analyses have been published previously in *Arthritis Care & Research* (7). Table 1 summarizes the psychometric properties of the 14 measures resulting from the steps above.

Membership survey. The 14 measures were then grouped (Disease Activity Score [DAS]/DAS with 28-joint counts [DAS28], Simplified Disease Activity Index [SDAI]/Clinical Disease Activity Index [CDAI], Patient Activity Scale [PAS] scores, Routine Assessment of Patient Index Data [RAPID] scores, Rheumatoid Arthritis Disease Activity Index 5, Chronic Arthritis Systemic Index, and patient global assessment of disease activity [PtGA]/provider global assessment of disease activity [PrGA]) and incorporated into a survey sent to practicing rheumatologists (n = 4,368); 335 recipients (7.7%) completed the survey. Most respondents (76.8%) were currently using a measurement tool in their clinical practice (see Supplementary Table 3, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). We weighted the survey results for region, sex, and age to adjust for the low response rate (see Supplementary Table 4, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Derivation of final recommendations. Based on the information gathered in the preceding phases, including psychometric analyses and physician ratings, the WG selected 6 measures for point-of-care RA disease activity

Table 1. Summary of RA disease activity measures recommended for point-of-care clinical use*

Measure/scale	Measure outputs	No. of items	Response format	Method of administration	Time for administration	Validated in RA	Psychometric properties†		
							Reliability	Validity	Responsiveness
Patient-driven composite tools									
PAS	A single score on a continuous scale (0–10)	3	HAQ: 0–3 Pain VAS: 0–10 Pt Global VAS: 0–10	Patient questionnaire	Patient: <3.5 minutes Provider: <1 minute Lab: N/A	Yes	Acceptable; test–retest reliability for composite has not been evaluated	Acceptable	Acceptable for individual components
PAS-II	A single score on a continuous scale (0–10)	3	HAQ-II: 0–3 Pain VAS: 0–10 Pt Global VAS: 0–10	Patient questionnaire	Patient: <1.5 minutes Provider: <30 seconds Lab: N/A	Yes	Acceptable; test–retest reliability for composite has not been evaluated	Acceptable	Acceptable for individual components
RAPID-3	A single score on a continuous scale (0–10)	3	MDHAQ: 0–3 Pain VAS: 0–10 Pt Global VAS: 0–10	Patient questionnaire	Patient: ≈1.5 minutes Provider: <30 seconds Lab: N/A	Yes	Acceptable; test–retest reliability for composite has not been evaluated	Good	Acceptable for individual components
Patient and provider composite tool									
CDAI	A single score on a continuous scale (0–76)	4	28TJC: 0–28 28SJC: 0–28 Pt Global VAS: 0–10 Pr Global VAS: 0–10	Provider item; patient item	Patient: ≈10 seconds Provider: <2 minutes Lab: N/A	Yes	Good; test–retest reliability for composite has not been evaluated	Excellent	Excellent
Patient, provider, and laboratory composite tools									
DAS28 (ESR or CRP)	A single score on a continuous scale (0–9.4)	4, or 3 when general health is omitted	28TJC: 0–28 28SJC: 0–28 ESR: 0–100 or CRP with lower detection level of 1.0 mg/liter Pt Global VAS: 0–100	Provider assessment; patient item; lab	Patient: ≈10 seconds Provider: 3–5 minutes Lab: 1 hour waiting time for ESR	Yes	Excellent	Excellent	Excellent
SDAI	A single score on a continuous scale (0–86)	5	28TJC: 0–28 28SJC: 0–28 Pt Global VAS: 0–10 CRP: 0–10	Provider item; patient item; lab	Patient: ≈10 seconds Provider: ≈2 minutes Lab: waiting time for CRP varies by lab	Yes	Good; test–retest reliability for composite has not been evaluated	Excellent	Excellent

* Measures are not shown in order of preference. RA = rheumatoid arthritis; PAS = Patient Activity Scale; HAQ = Health Assessment Questionnaire; VAS = visual analog scale; Pt Global VAS = patient global assessment of disease activity VAS; Lab = laboratory value required; N/A = not applicable; RAPID-3 = Routine Assessment of Patient Index Data with 3 measures; MDHAQ = Multidimensional HAQ; CDAI = Clinical Disease Activity Index; 28TJC = 28 tender joint count; 28SJC = 28 swollen joint count; Pr Global VAS = provider global assessment of disease activity VAS; DAS28 = Disease Activity Score with 28-joint counts; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; SDAI = Simplified Disease Activity Index.
† Psychometric properties were subjectively ranked using an ordered category scale (excellent, good, acceptable, poor, and unacceptable) based on currently published literature.

Table 2. Required components of rheumatoid arthritis disease activity measures recommended for point-of-care clinical use*

	Physician joint count	Patient global VAS	Provider global VAS	HAQ version	Pain	Defined remission criteria
Patient-driven composite tools						
PAS		●		HAQ	●	●
PAS-II		●		HAQ-II	●	●
RAPID-3		●		MDHAQ	●	●
Patient and provider composite tool						
CDAI	●	●	●	N/A		●
Patient, provider, and laboratory composite tools						
DAS28 (ESR or CRP)	●	●		N/A		●
SDAI	●	●	●	N/A		●

* Measures are not shown in order of preference. VAS = visual analog scale; HAQ = Health Assessment Questionnaire; PAS = Patient Activity Scale; RAPID-3 = Routine Assessment of Patient Index Data with 3 measures; MDHAQ = Multidimensional HAQ; CDAI = Clinical Disease Activity Index; N/A = not applicable; DAS28 = Disease Activity Score with 28-joint counts; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; SDAI = Simplified Disease Activity Index.

measurement: the CDAI, DAS28 (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]), PAS, PAS-II, RAPID-3, and SDAI (Table 2).

Discussion

Since the 1950s, when the first composite disease activity measurement tool for use in RA was developed (8), many attempts have been made to improve RA disease activity monitoring. Of the 63 currently available RA disease activity measurement tools, we used a multistep process to progressively filter down to 6 recommended measures: the CDAI, DAS28 (ESR or CRP), PAS, PAS-II, RAPID-3, and SDAI. All 6 produce a single continuous index and have defined ranges for indicating low, moderate, or high disease activity or clinical remission (Table 3). By applying these tools systematically in clinical practice, physicians will be able to "treat to target" and effectively implement the ACR recommendations for the treatment of RA (9).

Realizing the heterogeneity of settings in which health care is delivered to patients with RA in the US, we selected measures that offer a full range of data collection options. Some are purely patient reported (PAS, PAS-II, and RAPID-3), some add provider assessment (CDAI), and some add provider assessment and laboratory acute-phase reactants (SDAI and DAS28). Below we summarize the key features of each measure to allow those caring for patients with RA to select the one best suited to their clinical practice.

Patient-driven composite tools (PAS [10], PAS-II [10], and RAPID-3 [11]) have the advantage of being relatively easy to use in clinical practice because they do not require provider assessments such as formal joint counts (tender or swollen). Patients can often complete these measures on standardized paper or electronic forms in the waiting room, making them very practical to use.

There are 3 core components to each of the patient-driven measures: visual analog scale patient pain score (12), PtGA (12), and a measure of functional assessment. Since 2 of 3 components are similar across these measures, the distinguishing feature is the functional assessment tool (PAS includes the Health Assessment Questionnaire [HAQ] [13], PAS-II includes the HAQ-II [10,14], and RAPID-3 uses the Multidimensional HAQ [MDHAQ] [15]). In choosing a measure, providers may want to consider the length (the MDHAQ in RAPID-3 and the HAQ-II in PAS-II are 10 items each, while the original HAQ in PAS is 41 items) and psychometric properties of each functional assessment tool, discussed briefly below. For a more detailed review of the psychometric properties of the 3 patient-driven disease

Table 3. Disease activity cutoffs for each American College of Rheumatology–recommended disease activity measure*

Disease activity measure	Scale	Remission	Low/minimal	Moderate	High/severe
Patient-driven composite tools					
PAS	0–10	0.00–0.25	0.26–3.70	3.71 to <8.0	8.00–10.00
PAS-II	0–10	0.00–0.25	0.26–3.70	3.71 to <8.0	8.00–10.00
RAPID-3	0–10	0–1.0	>1.0 to 2.0	>2.0 to 4.0	>4.0 to 10
Patient and provider composite tool					
CDAI	0–76	≤2.8	>2.8 to 10.0	>10.0 to 22.0	>22.0
Patient, provider, and laboratory composite tools					
DAS28 (ESR or CRP)	0–9.4	<2.6	≥2.6 to <3.2	≥3.2 to ≤5.1	>5.1
SDAI	0–86	≤3.3	>3.3 to ≤11.0	>11.0 to ≤26	>26

* PAS = Patient Activity Scale; RAPID-3 = Routine Assessment of Patient Index Data with 3 measures; CDAI = Clinical Disease Activity Index; DAS28 = Disease Activity Score with 28-joint counts; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; SDAI = Simplified Disease Activity Index.

Table 4. Formulas for measurement tools*

Measurement tool	Formula	Online source
CDAI	28SJC + 28TJC + PrGA + PtGA	http://www.rheumatology.org/CDAI
DAS28		
DAS28-ESR	$0.56 \times \sqrt{(28TJC)} + 0.28 \times \sqrt{(28SJC)} + 0.70 \times \ln(ESR) + 0.014 \times PtGA$	http://www.das-score.nl/
DAS28-CRP	$0.56 \times \sqrt{(28TJC)} + 0.28 \times \sqrt{(28SJC)} + 0.36 \times \ln(CRP + 1) + 0.014 \times PtGA + 0.96$	http://www.das-score.nl/
PAS	(HAQ × 3.33 + pain VAS + PtGA VAS)/3	http://www.arthritis-research.org/research/pas
PAS-II	(HAQ-II × 3.33 + pain VAS + PtGA VAS)/3	http://www.arthritis-research.org/research/pas
RAPID-3	(MDHAQ × 3.33 + pain VAS + PtGA VAS)/3	http://mdhaq.org/Public/Questionnaires.aspx
SDAI	28SJC + 28TJC + PrGA + PtGA + CRP	http://www.rheumatology.org/SDAI

* Numerical rating scales may be substituted for visual analog scales (VAS) in all measures. CDAI = Clinical Disease Activity Index; 28SJC = 28 swollen joint count; 28TJC = 28 tender joint count; PrGA = provider global assessment of disease activity; PtGA = patient global assessment of disease activity; DAS28 = Disease Activity Score with 28-joint counts; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; PAS = Patient Activity Scale; HAQ = Health Assessment Questionnaire; RAPID-3 = Routine Assessment of Patient Index Data with 3 measures; MDHAQ = Multidimensional HAQ; SDAI = Simplified Disease Activity Index.

activity measures, please refer to the recent assessment by Anderson et al (7).

All 3 measures take less than 3 minutes for patients to complete and have simple mathematical scoring. However, the RAPID-3 has been tested in many rheumatic diseases, not just RA, and therefore may be applied to patients more broadly in clinic practice. Beyond these practical issues, there are other issues related to the reliability and validity of these measures that should be considered. For example, although components of each of the 3 measures have been found to be reliable, valid, and sensitive to change, information is not available about how the composite score for each measure performs. Additionally, long-term outcomes regarding joint damage with these 3 measures have not been studied directly. Therefore, it is theoretically possible that the composite score may be less reliable, valid, or sensitive to change than its individual components.

Finally, patient-driven tools lack a formal joint assessment, something that is thought to lend face validity to a measure of RA disease activity (2). However, it is important to realize that the inclusion of provider joint counts is highly examiner dependent, and while fairly reproducible by a single assessor, may be unreliable if the assessor changes and may not correlate completely with sonographic evidence of synovitis (16,17). While patient-reported measures have important limitations, such as reflecting a patient's perception of their disease, which may be influenced by a variety of factors (e.g., cultural beliefs, self-efficacy, mood), they do produce a less random and more reliable measurement of change over time. In addition, some studies suggest that patient-reported measures predict long-term outcomes better than provider joint counts and acute-phase reactants (18–21). The formulas used to calculate each measurement tool are shown in Table 4.

The CDAI, a patient and provider composite tool (22), adds 3 components of the provider assessment (PrGA, 28 swollen joint count, and 28 tender joint count) to the PtGA. Designed as a simple numerical addition of the component scores, it avoids point-of-care issues such as needing a calculator to enter differentially weighted components. Further, it does not require an acute-phase reactant, enhancing its feasibility in some clinical settings since results are available in real time. The measure does require providers to perform detailed joint counts reliably and consistently.

Available studies show excellent psychometric properties, including validity and sensitivity to change. Although the components are reliable, it should be noted that the reliability of the composite measure is unknown.

The patient, provider, and laboratory composite tools (SDAI [23] and DAS28 [24]) have several components in common: provider tender and swollen joint counts, PtGA, and an acute-phase reactant. The main distinctions between these 2 measures are that the DAS28 does not include a PrGA and it requires a more complex calculation to arrive at a score based on differential weighting of individual indices (e.g., the DAS28 weighs tender joint count more heavily than swollen joint count).

The SDAI (like the CDAI) is a simpler numerical addition of individual components that are weighted evenly. Generally, the DAS28 uses the ESR (although the DAS28-CRP is also available) and the SDAI uses the CRP level. The SDAI is the most sensitive and specific for prediction of clinical decisions to change disease-modifying antirheumatic drugs, and an SDAI score $\leq$3.3 is one of two recommended definitions of remission by the ACR and the European League Against Rheumatism to be used in RA clinical trials (1). Although remission criteria for the DAS28 are less conservative than several other measures, including both the SDAI and CDAI, treating to a DAS28 target level of $\leq$2.4 has been shown to improve RA outcomes (3,25).

It is important to note that the inclusion of acute-phase reactants in these measures introduces a new set of variables, and therefore adds some complexity. The ESR contributes a sizeable portion (15%) of the information in the DAS28-ESR. Therefore, remission may be underestimated in high ESR states with few active joints. Similarly, in low ESR states, remission criteria may be met but patients may still have a significant number of swollen joints (26,27). Like the DAS28-ESR, it has been shown that DAS28-CRP scores may also incorrectly estimate remission as they are

generally lower than DAS28-ESR scores (28). Another consideration is that newer biologic agents that target specific inflammatory cytokines are differentially reflected in the ESR and CRP and may therefore disproportionately deflate the composite score.

In addition, inclusion of acute-phase reactants in the DAS28 and SDAI complicates the logistics and timing of using these measures in point-of-care clinical decision making. Although these measures have traditionally been used in clinical trials, academic medical centers, and large multispecialty clinics, logistical barriers have likely delayed their widespread adoption in smaller practice settings.

ACR members responding to our survey rated the PtGA and PrGA as the most feasible tools for use in clinical practice. However, these measures are not included in the final set of selected measures. Limitations of these measures include the lack of standardization in structure (e.g., horizontal and vertical visual analog scale, anchored versus unanchored lines, boxes or circles) and the paucity of well-defined disease activity categories, which are important in creating thresholds for clinical decision making and for quality reporting.

The WG recognizes that there is currently no ideal measure of disease activity, and acknowledges that some measures excluded in our review may later be found to possess adequate, or even superior, psychometric properties to the 6 recommended measures. In the absence of head-to-head comparisons of the different disease activity tools, we had to rely on a process that involved a combination of expert opinion and literature review to select measures. Nevertheless, based on available evidence and expert opinion, we believe we have identified measures that are currently the most reliable, valid, feasible, and acceptable measures of disease activity in RA.

It is important to note that we made no attempt to perform de novo psychometric analyses on measures and restricted our work to reviewing published literature. In addition, our survey of the ACR membership had a low response rate. This may signal that few clinicians currently measure RA disease activity systematically, or that most feel unqualified to rate the utility of different measurement tools. To partially address the low response rate, we weighted the characteristics of the responders versus those of nonresponders for region, sex, and age. These weighted responses suggest that the responders were generally representative of the ACR membership on the examined characteristics.

Finally, although remission is the ultimate therapeutic goal in RA, remission and even attainment of low disease activity may not be appropriate targets for all patients due to comorbid conditions, treatment toxicity, and patient preference. In addition, some measure components are influenced by comorbid conditions that elevate acute-phase reactants or result in tender joints (e.g., fibromyalgia) (2). Despite these complexities, standardized assessment of disease activity in RA facilitates treating to target, which has been shown to improve disease outcomes (2).

The CDAI, DAS28 (ESR or CRP), PAS, PAS-II, RAPID-3, and SDAI all accurately reflect disease activity; are sensitive to change; discriminate between low, moderate, and high disease activity states; are feasible to perform at the point of care; and are acceptable to most practicing rheumatologists. Above we have outlined our methods for arriving at these recommended measures and summarized some of the key features that clinicians should consider when choosing a measure to adopt in their clinical practice. Incorporation of these validated RA disease activity measures into a practice's workflow will facilitate adherence to the ACR guidelines for the treatment of RA and provide the necessary tools for treating to target. Moreover, routine use of these measures will allow clinicians to demonstrate that they are providing high-quality care for RA, as measured by nationally endorsed quality measures.

ACKNOWLEDGMENTS

We thank Harlan Sayles, University of Nebraska Medical Center, Omaha, Nebraska, for statistical analysis of the member survey, and all those who participated in the surveys performed as part of this project. We also thank Amy Miller, American College of Rheumatology, Atlanta, Georgia, for editorial assistance.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kazi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Anderson, Caplan, Neogi, Michaud, Saag, O'Dell, Kazi.

Acquisition of data. Anderson, Kazi.

Analysis and interpretation of data. Anderson, Caplan, Yazdany, Robbins, Neogi, Michaud, O'Dell, Kazi.

ADDITIONAL DISCLOSURE

Dr. Anderson is currently employed by Abbott Laboratories but was not at the time of the study. Abbott Laboratories had no financial interest in this project and had no input in the design, content, data collection, or analysis, and had no role in the writing or approval of this article, with all opinions and conclusions expressed herein those of the authors.

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ARTHRITIS & RHEUMATISM
Vol. 62, No. 9, September 2010, pp 2569–2581
DOI 10.1002/art.27584
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Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and www.interscience.wiley.com

2010 Rheumatoid Arthritis Classification Criteria

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an external data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

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Objective. **The 1987 American College of Rheumatology (ACR; formerly, the American Rheumatism Association) classification criteria for rheumatoid arthritis (RA) have been criticized for their lack of sensitivity in early disease. This work was undertaken to develop new classification criteria for RA.**

Methods. **A joint working group from the ACR and the European League Against Rheumatism devel-**

This article is published simultaneously in the September 2010 issue of *Annals of the Rheumatic Diseases*.

Supported by the American College of Rheumatology and the European League Against Rheumatism.

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oped, in 3 phases, a new approach to classifying RA. The work focused on identifying, among patients newly presenting with undifferentiated inflammatory synovitis, factors that best discriminated between those who were and those who were not at high risk for persistent and/or erosive disease—this being the appropriate current paradigm underlying the disease construct "rheumatoid arthritis."

Results. **In the new criteria set, classification as "definite RA" is based on the confirmed presence of synovitis in at least 1 joint, absence of an alternative diagnosis that better explains the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in 4 domains: number and site of involved joints (score range 0–5), serologic abnormality (score range 0–3), elevated acute-phase response (score range 0–1), and symptom duration (2 levels; range 0–1).**

Conclusion. **This new classification system redefines the current paradigm of RA by focusing on features at earlier stages of disease that are associated with persistent and/or erosive disease, rather than defining the disease by its late-stage features. This will refocus attention on the important need for earlier diagnosis and institution of effective disease-suppressing therapy to prevent or minimize the occurrence of the undesirable sequelae that currently comprise the paradigm underlying the disease construct "rheumatoid arthritis."**

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality (1–5). Given

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Dr. Aletaha has received consulting fees, speaking fees, and/or honoraria from Abbott, Bristol-Myers Squibb, UCB, Schering-Plough, Wyeth, and Roche (less than $10,000 each). Dr. Bingham has received consulting fees, speaking fees, and/or honoraria from UCB, Roche, Genentech, Celgene, and Merck Serono (less than $10,000 each); he has received research and/or educational grant support from Bristol-Myers Squibb, Genentech, UCB, Centocor, Abbott, and Amgen. Dr. Birnbaum has received consulting fees, speaking fees, and/or honoraria from Amgen, Pfizer, Centocor, Abbott, and UCB (less than $10,000 each). Dr. Burmester has received consulting fees, speaking fees, and/or honoraria from Abbott, Bristol-Myers Squibb, Pfizer, UCB, and Roche (less than $10,000 each). Dr. Bykerk has received consulting fees, speaking fees, and/or honoraria from Amgen, Wyeth, Abbott, Schering-Plough, Roche, Bristol-Myers Squibb, and UCB (less than $10,000 each); her spouse is employed by Genzyme and owns stock in the company. Dr. Cohen has received consulting fees, speaking fees, and/or honoraria from UCB, Genentech, Bristol-Myers Squibb, and Human Genome Sciences (less than $10,000 each). Dr. Combe has received consulting fees, speaking fees, and/or honoraria from Abbott, Bristol-Myers Squibb, Pfizer, Roche, Schering-Plough, and Merck, Sharpe, and Dohme (less than $10,000 each). Dr. Emery has received consulting fees, speaking fees, and/or honoraria from Pfizer, Abbott, Centocor, UCB, Roche, Bristol-Myers Squibb, and Merck, Sharpe, and Dohme (less than $10,000 each). Dr. Ferraccioli holds a patent for T cell receptor clonotype analysis (PCT/IB 2008/053152 NP). Dr. Huizinga has received consulting fees, speaking fees, and/or honoraria from Schering-Plough, Bristol-Myers Squibb, UCB, Biotest AG, Wyeth/Pfizer, Novartis, Roche, Sanofi-Aventis, Abbott, and Axis-Shield (less than $10,000 each). Dr. Kavanaugh has conducted clinical research for Amgen, Abbott, Bristol-Myers Squibb, UCB, Roche, Centocor, Genentech, and Sanofi-Aventis. Dr. Kay has received consulting fees from Array BioPharma, Bristol-Myers Squibb, Celgene, Centocor, Genentech, Roche, UCB, and Sanofi-Aventis (less than $10,000 each). Dr. Mease has received consulting fees, speaking fees, and/or honoraria from Abbott, Amgen, Biogen Idec, Bristol-Myers Squibb, Centocor, Roche, Genentech, UCB, Pfizer, Novartis, and Eli Lilly (less than $10,000 each). Dr. Ménard has received unrestricted educational and research grants as well as consulting and speaking fees from Abbott, Amgen, Inova, Merck, Pfizer, Roche, Schering-Plough, UCB, and Wyeth (less than $10,000 each) and investigator-initiated research grants from Bristol-Myers Squibb, EuroImmun AG, and Roche (more than $10,000 each); he owns stock or stock options in Merck; and he has a license agreement with EuroImmun AG for an anti-Sa enzyme-linked immunosorbent assay. Dr. Moreland has received consulting fees, speaking fees, and/or honoraria from Biogen Idec, Centocor, Pfizer, Takeda, KaloBios, ChemoCentryx, UCB, Genentech, Incyte, and Eli Lilly (less than $10,000 each). Dr. Naden has received consulting fees from the American College of Rheumatology in regard to the methodology of developing weighted scoring systems (more than $10,000). Dr. Pincus has received consulting fees, speaking fees, and/or honoraria from Amgen, Abbott, Bristol-Myers Squibb, Centocor, UCB, Wyeth, and Genentech (less than $10,000 each) and investigator-initiated research grants from Amgen, Bristol-Myers Squibb, UCB, and Centocor. Dr. Stanislawska-Biernat has received speaking fees from Abbott and Pfizer (less than $10,000 each). Dr. Vencovský has received speaking fees from Pfizer, UCB, Abbott, Roche, and Merck, Sharpe, and Dohme (less than $10,000 each).

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Submitted for publication January 22, 2010; accepted in revised form May 20, 2010.

the presence of autoantibodies, such as rheumatoid factor (RF) and anti–citrullinated protein antibody (ACPA) (tested as anti–cyclic citrullinated peptide [anti-CCP]), which can precede the clinical manifestation of RA by many years (6–9), RA is considered an autoimmune disease (10,11). Autoimmunity and the overall systemic and articular inflammatory load drive the destructive progression of the disease. However, although structural changes, which can be visualized by conventional radiography or other imaging techniques, best distinguish RA from other arthritic disorders (12), joint damage is rarely apparent in the very early stages of disease, but rather accumulates consistently over time (13–16).

Over the last decade, the optimal use of disease-modifying antirheumatic drugs (DMARDs), in particular the anchor DMARD methotrexate (MTX) (17–19), and the availability of new biologic agents (11,20), have dramatically enhanced the success of RA management. Moreover, it has been recognized that early therapeutic intervention improves clinical outcomes and reduces the accrual of joint damage and disability (21–23). Undoubtedly, treating patients at a stage at which evolution of joint destruction can still be prevented would be ideal. However, at present, clinical trials of RA treatments are hampered by lack of criteria allowing for study enrollment of patients at early stages of disease. Thus, to date it has not been possible to effectively investigate the efficacy of early interventions in terms of their ability to prevent later-stage RA, since there are no validated or accepted uniform criteria to classify such individuals with early disease.

The standard and accepted means of defining RA is by use of classification criteria. Classification criteria enable the stratification of groups of individuals into those with and those without RA in order to standardize recruitment into clinical trials and related studies, and provide the basis for a common approach to disease definition that can be used to compare across studies and centers. The classification criteria set that is in widespread international use to define RA is the 1987 American College of Rheumatology (ACR; formerly the American Rheumatism Association) criteria (24). These criteria are well accepted as providing the benchmark for disease definition, but have a significant limitation in that they were derived by trying to discriminate patients with established RA from those with a combination of other definite rheumatologic diagnoses. They are therefore not helpful in achieving the goal of identifying patients who would benefit from *early* effective intervention, as discussed above. Indeed, with modern therapies, the goal is to prevent individuals from reaching the chronic, erosive disease state that is exemplified in the 1987 criteria for RA.

A joint working group of the ACR and the European League Against Rheumatism (EULAR) was therefore formed to develop a new approach for classification of RA. While classification criteria are potentially adopted for use as aids for diagnosis, the focus of this endeavor was not on developing diagnostic criteria or providing a referral tool for primary care physicians. Indeed, a separate body of work is needed to develop such tools, which may be informed by classification criteria. Thus, the specific charge was to develop new classification criteria for RA to facilitate the study of persons at earlier stages of the disease. It was with this framework in mind that the working group developed the 2010 ACR/EULAR classification criteria for RA.

Overview on hypothesis and methods of Phases 1 and 2

A priori, the working group focused on developing an approach that would be appropriate for newly presenting patients with undifferentiated inflammatory synovitis, in order to identify that subset of patients who are at sufficiently high risk of persistent and/or erosive disease—this being the appropriate current paradigm underlying the disease construct "rheumatoid arthritis"—to be classified as having RA. It was recognized that such a scheme should not be developed using existing criteria sets as the "gold standard," because of the inherent circularity. The goal set forth was to develop a set of rules to be applied to newly presenting patients with undifferentiated synovitis that would 1) identify the subset at high risk of chronicity and erosive damage; 2) be used as a basis for initiating disease-modifying therapy; and 3) not exclude the capture of patients later in the disease course.

To achieve these goals, the working group devised a 3-phase program. Phase 1 was a data-driven approach based on cohorts of real-world patients with early arthritis, to identify factors, and their relative weights, that were associated with the subsequent decision by a physician to start MTX treatment. Phase 2 was a consensus-driven, decision science–based approach, informed by the data from Phase 1, to refine these factors and their weights using a series of "paper patients," as well as to identify any other factors that may be of relevance based on current clinical thinking. Phase 3, which is the focus of this report, describes the derivation, from the previous 2 phases, of the final

Table 1. Summary of Phase 1 results*

Variable	Comparison	Relative weight†
Swollen MCP joint	Present vs. absent	1.5
Swollen PIP joint	Present vs. absent	1.5
Swollen wrist	Present vs. absent	1.6
Hand tenderness	Present vs. absent	1.8
Acute-phase response	Low-level abnormal vs. normal	1.2
	Highly abnormal vs. normal	1.7
Serology	Low-positive vs. negative	2.2
(RF or ACPA)	High-positive vs. negative	3.9

* MCP = metacarpophalangeal; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody.
† Derived from odds ratios from the multivariate regression model, and interpreted as the increase in the odds of having rheumatoid arthritis (RA) with as opposed to without the respective feature (e.g., weight of 1.5 for swelling of proximal interphalangeal [PIP] joints means that the odds of having RA is 1.5-fold in patients with as opposed to patients without swelling of a PIP joint).

classification criteria set. The details of the methods and results from Phases 1 and 2 are provided elsewhere (25,26), and are briefly summarized below.

Phase 1. The aim of Phase 1 was to identify the contributions of clinical and laboratory variables that in practice were the most predictive of the decision to initiate DMARD therapy in a population of patients with early undifferentiated synovitis. Initiation of DMARD therapy was used as an indicator of the physician's opinion that the patient was at risk of developing persistent and/or erosive arthritis that we would currently consider to be RA. Data on 3,115 patients from 9 early arthritis cohorts who were considered not to have evidence of another possible diagnosis explaining their presentation were obtained. Between July 2007 and November 2008 an expert working group developed an analysis strategy that related an agreed-upon list of standardized clinical and laboratory variables collected at baseline to the initiation of DMARD treatment within the next 12 months. MTX initiation was used as the gold standard for this purpose. The analytical process aimed to identify the independent contribution of each variable on this list and included univariate regression modeling, a subsequent principal components analysis, and a multivariate regression model that included all identified components (25). The resulting list of informative variables identified during that process and the weights based on the odds ratios are shown in Table 1.

Phase 2. Phase 2 consisted of a consensus-based, decision science–informed approach, which took place between November 2008 and June 2009. The purpose of this phase was to derive a clinician-based judgment on the relative contribution of clinical and laboratory factors deemed to be important in influencing the probability of developing "persistent inflammatory and/or erosive arthritis that is currently considered to be RA" (hereinafter referred to as "developing RA").

An expert panel was assembled, comprising 12 rheumatologists from Europe and 12 from North America with extensive experience in the diagnosis and management of RA. They provided real-life case scenarios of patients with early undifferentiated inflammatory arthritis representing low to high probability of developing RA. A 2-day workshop was held in May 2009 in which domains (factors) and categories within those domains that were important in determining the probability of developing RA were identified. When appropriate, these judgments were informed by the results of Phase 1 and other available literature. The relative importance or weights of these domains and their categories were determined by means of decision science theory and conjoint adaptive technology, using the computerized 1000Minds program (www.1000minds.com) in an interactive and iterative process (26). This analysis permitted the calculation of an individual's score of the likelihood of developing RA from 0 to 100, where a higher score indicated greater likelihood of RA development. The domains, categories, and weights derived during that initial process are shown in Table 2.

Objectives, methods, and results of Phase 3

Objectives of Phase 3. In Phase 3 the working group integrated the findings of the first 2 phases, refined the scoring system, and determined the optimal cut point to define "definite RA." The goal of this final phase was to utilize the results of Phases 1 and 2 to develop a scoring system that would be applicable to *newly* presenting patients with undifferentiated inflammatory arthritis to permit identification of those with a high probability of developing persistent and/or erosive RA. Being intended for use with newly presenting patients, the scoring system should be robust enough that it could be applied repeatedly during the early course of disease, such that a patient identified as not classifiable as having definite RA at initial presentation might be classified as having definite RA at a subsequent time point. The work was not aimed at classifying subjects with established disease, either active or inactive. However, the working group recognized that patients may present for the first time with disease that is at a later stage and being treated. Thus, although it was not the explicit charge of the working group to provide

Table 2. Summary of Phase 2 results and subsequent modifications

	Exact (0−100)	Rescaled (0−10)	Rounded to 0.5 (0−10)
Joint involvement*			
1 large	0	0	0
>1−10 large, asymmetric	10.2	1.02	1
>1−10 large, symmetric	16.1	1.61	1.5
1−3 small	21.2	2.12	2
4−10 small	28.8	2.88	3
>10, including at least 1 small joint	50.8	5.08	5
Serology†			
Negative RF *and* negative ACPA	0	0	0
Low-positive RF *or* low-positive ACPA	22.0	2.20	2
High-positive RF *or* high-positive ACPA	33.9	3.39	3.5
Acute-phase reactants‡			
Normal CRP *and* normal ESR	0	0	0
Abnormal CRP *or* abnormal ESR	5.9	0.59	0.5
Duration of symptoms§			
<6 weeks	0	0	0
≥6 weeks	9.3	0.93	1

* Joint involvement refers to any *swollen* or *tender* joint on examination. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of the involved joints, with placement into the highest category possible based on the pattern of joint involvement. "Large joints" refers to shoulders, elbows, hips, knees, and ankles. "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists. "Symmetric" is defined as bilateral involvement of at least 1 region. In the category ">10 joints," at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti−citrullinated protein antibody.

‡ Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

rules for the classification of such patients, it is appropriate to have a single criteria system that could be applied to all patients; these issues were addressed by the expert panel during Phase 3.

Determination of the optimal cut point for definite rheumatoid arthritis. Determination of the optimal cut point to classify an individual as having definite RA was achieved using 2 complementary approaches, mirroring the approaches used in the first 2 phases: data-informed and consensus-based. From the consensus-based approach, the expert panel was asked to examine the rankings of case scenarios based on the new scoring system and to indicate, in their opinion, the point at which the cases changed from "probable" to "definite" RA. Four cases were excluded due to missing domain information (n = 2) or ineligibility (2 cases were more likely another diagnosis). For the remaining 50 cases, the mean cut point defining definite RA was 65.7 (median 66.1; range 60.0–70.3) of a total possible score of 100.

A data-driven verification of that cut point was then attempted, in which the new scoring system was applied to 3 of the existing cohorts used for Phase 1 (the Etude et Suivi des Polyarthrites Indifferenciees Recentes data set from France, the Norwegian data set, and the Rotterdam Early Arthritis Cohort data set from Rotterdam) (25). These cohorts were chosen based on the completeness of data and the collected variables, enabling calculation of the patients' probability scores at baseline. The disease characteristics of these cohorts were not substantively different from those of the remaining cohorts (data not shown).

The area under the curve (AUC) for the 3 receiver operating characteristic (ROC) curves (which plot sensitivity against 1 − specificity for the range of scores) indicated good discrimination of those who did versus those who did not receive MTX (or another DMARD/biologic agent) within a year (AUC 0.82 for Norway, 0.66 for France, and AUC 0.69 for Rotterdam; $P < 0.0001$ for all). The probability scores similarly discriminated between those who fulfilled the 1987 ACR criteria at 12 months and those who did not (AUC for the ROC curves 0.88 [Norway], 0.67 [France], and 0.72 [Rotterdam]). Visual inspection of the diagnostic test parameters associated with curves that used MTX initiation as the outcome showed a maximum slope for both the positive and negative likelihood ratios between a score of 60/100 and 70/100, with flattening thereafter (67 in the Norway cohort, 66 in the French cohort, and 66 in the Rotterdam cohort). The cut point of 60–70 that was derived from expert consensus was therefore supported by these data. Given the consistency with the consensus-based approach, and to maximize sensitivity of the criteria, a cut point of 60 was deemed to be most appropriate.

Rationale for the composition and weight of the final criteria. For development of the final criteria set, the results and weights from the comprehensive Phase 2 process (26) were used as a starting point. Based on

Table 3. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2−10 large joints	1
1−3 small joints (with or without involvement of large joints)#	2
4−10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

† Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡ Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§ Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti−citrullinated protein antibody.

‡‡ Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

these categories and weights, we aimed in the final steps of the project to simplify the criteria in order to ensure that they were user friendly. We used the results of the data-driven Phase 1 as a guide for these adaptations, and verified at each step that the main properties of the criteria were not altered and that classification of patients remained unchanged.

The general steps toward simplification are shown

in Table 2, and included rescaling the scoring system to a scale of 0–10. Then, each of the category weights was rounded to multiples of 0.5. We tested the rounded scoring system in the case scenarios that had been used in Phase 2, and found no changes in the ranking of the cases compared with the exact scale. According to the rescaling, the cut point for definite RA would be ≥6/10.

Despite their slightly different weights, the categories of asymmetric and symmetric oligoarthritis of large joints were merged for several reasons: first, symmetry was not found to be significantly important in the data analysis during Phase 1 (25), and second, the impact of merging was minimal when all possible presentations of patients with symmetric or asymmetric large joint inflammation were explored. For simplicity and ease of use, an integer scale was sought for all components of the scoring system. Thus, the high positive serology category was rounded from 3.5 (originally 3.39) to an integer of 3 because in no instance would classification status be altered by this change. Additionally, the weight for abnormal acute-phase response was rounded from 0.5 (originally 0.59) to 1, based on the stronger weight of acute-phase response (and of high-level acute-phase response) in Phase 1 (25).

Validation of the final criteria set. The final criteria set with its simplified scoring system was further validated. Using the Phase 2 patient case scenarios, the correlation between cases' mean derived probability scores (0–100) and the proportion of expert panel members who indicated that they would initiate treatment with MTX out of concern about risk for persistence and/or erosive damage was strong (Spearman's r = 0.82, $P < 0.0001$). The correlation of score with the proportion of experts who would refer the patient to a trial of a new biologic agent with inherent risks was similarly strong (Spearman's r = 0.0.85, $P < 0.0001$).

As a further validation, 3 cohorts that were not used in the identification of factors from Phase 1 were studied (Leiden [The Netherlands], Leeds [UK], and Toronto [Canada]); their characteristics were not substantively different from those of the remaining cohorts (25). Among cohort participants who received MTX within a year from symptom onset, the proportions with a score of ≥6/10 were 96.8% (Leiden), 90.5% (Leeds), and 87.2% (Toronto).

Eligibility for testing with the new criteria. The classification criteria can be applied to any patient or otherwise healthy individual, as long as 2 mandatory requirements are met: first, there must be evidence of currently active clinical synovitis (i.e., swelling) in at least 1 joint as determined by an expert assessor (Table 3). All joints of a full joint count may be assessed for this purpose with the exception of the distal interphalangeal (DIP) joints, the first metatarsophalangeal (MTP) joint, and the first carpometacarpal (CMC) joint, since these joints are typically involved in osteoarthritis. Although currently no methods other than clinical examination should be used to evaluate the presence of synovitis in this determination of eligibility, this may change in the future as validated imaging techniques become more widely available. Second, the criteria may be applied only to those patients in whom the observed synovitis is not better explained by another diagnosis (Table 3). For example, conditions that should be considered and excluded include systemic lupus erythematosus, psoriatic arthritis, and gout, among others.

Classification criteria for RA. Four additional criteria can then be applied to eligible patients, as defined above, to identify those with "definite RA"; these are shown in Table 3. Application of these criteria provides a score of 0–10, with a score of ≥6 being indicative of the presence of definite RA. This final scoring system was derived from both Phase 1 and Phase 2 data. A patient with a score below 6 cannot be classified as having definite RA, but might fulfill the criteria at a later time point. Figure 1 depicts a tree algorithm that incorporates the weights of each domain and the cut point of 6 for classification as definite RA. To classify a patient as having or not having definite RA, a history of symptom duration, a thorough joint evaluation, and at least 1 serologic test (RF or ACPA) and 1 acute-phase response measure (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) must be obtained. It is acknowledged that an individual patient may meet the definition of RA without requiring that all tests be performed. For example, patients with a sufficient number of joints involved and longer duration of symptoms will achieve 6 points regardless of their serologic or acute-phase response status. However, for the purposes of clinical research and trial enrollment, documentation of each domain will be necessary for phenotyping.

Other clinical presentations: erosions and late disease. Because the aim of the new classification criteria is to enable diagnosis and treatment earlier in the course of disease to prevent disease complications, erosions were not considered for inclusion in the scoring system. However, as stated above, the working group recognized that patients may present at later stages of disease. Additionally, a single criteria system that could be applied to all patients was desired. Therefore, in addition to those who are newly presenting, 3 other

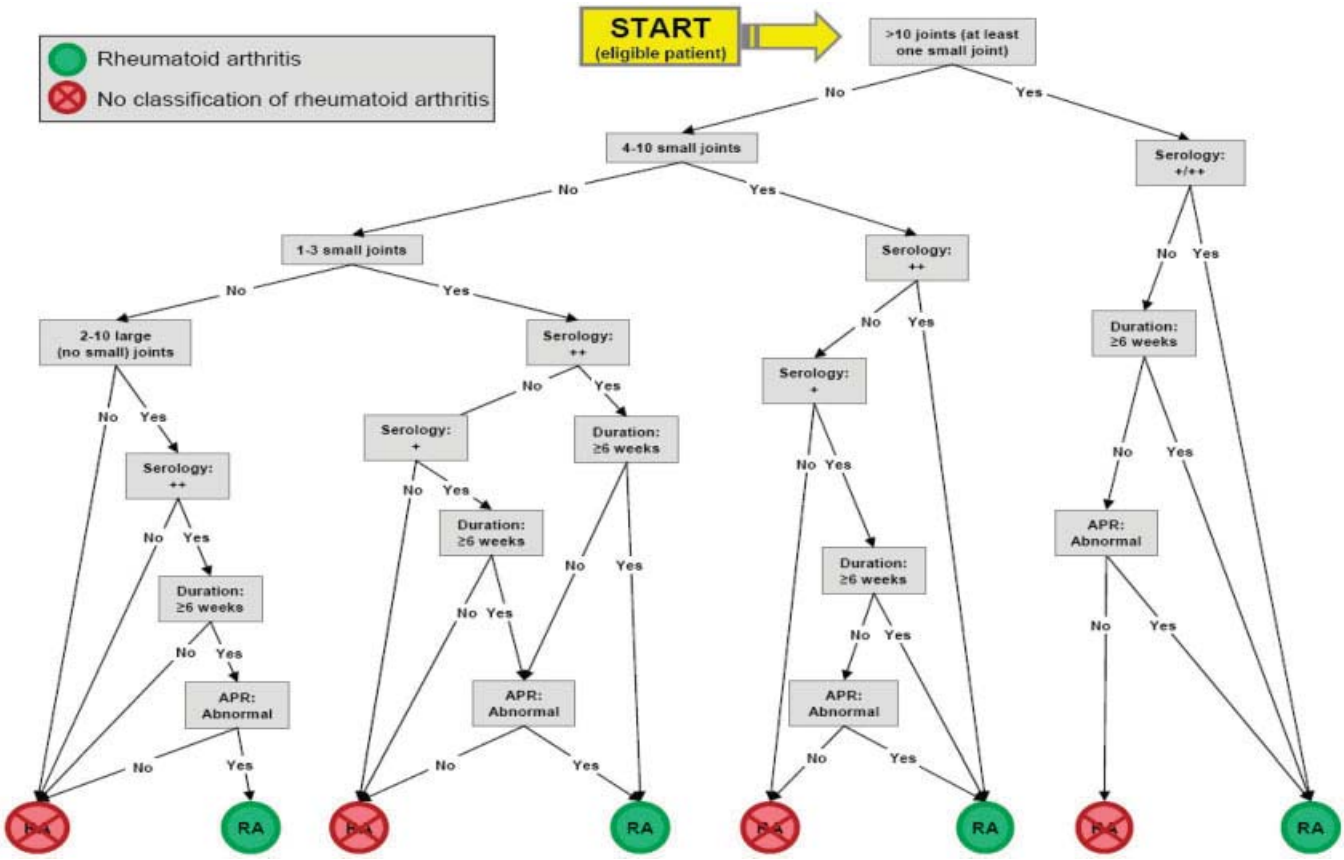

Figure 1. Tree algorithm for classifying definite rheumatoid arthritis (RA) (green circles) or for excluding its current presence (red circles) among those who are eligible to be assessed by the new criteria. APR = acute-phase response. Serology: + = low-positive for rheumatoid factor (RF) or anti–citrullinated protein antibody (ACPA); serology: ++ = high-positive for RF or ACPA; serology: +/++ = serology either + or ++. See footnotes to Table 3 for further explanation of categories.

groups of patients had to be considered: 1) those with erosions typical for RA were deemed to have prima facie evidence of RA and can be classified as such; 2) those with longstanding disease, either active or inactive, who, based on retrospectively available data, can be determined to have previously satisfied the classification criteria can similarly be classified as having definite RA; and 3) in the setting of early disease that is being treated, subjects may not fulfill the new criteria at initial presentation, but may do so as their condition evolves over time.

Glossary of definitions

In this section, we provide the detailed definitions necessary to correctly and accurately apply the new classification criteria for RA. A brief version of the glossary is included in the footnotes to Table 3.

Definition of an "involved" joint. Joint involvement, as used for the determination of pattern of joint distribution, differs from the definition of synovitis in 1 joint needed for eligibility in the eligibility criteria (see above): here it refers to any joint with swelling or tenderness on examination that is indicative of active synovitis. Tenderness is included as an equally important feature as swelling for the determination of joint involvement, particularly for the second through fifth MTP joints, in order to maximize sensitivity. Again, the DIP joints, the first MTP joint, and the first CMC joint should not be considered, given their prevalent involvement in osteoarthritis. Further, any joints with known

recent injury that could contribute to swelling or tenderness should not be considered. Additional evidence of joint activity from other imaging techniques (such as magnetic resonance imaging or ultrasound) may be used for confirmation of the clinical findings.

Definition of small joints. Small joints include the metacarpophalangeal, proximal interphalangeal (PIP), second through fifth MTP, and thumb IP joints, and the wrists. They do not include the first CMC, first MTP, or DIP joints, which are often affected by osteoarthritis.

Definition of large joints. The term "large joints" refers to the shoulders, elbows, hips, knees, and ankles.

Determination of the joint pattern category. Patients are categorized according to the number and location of involved joints by placing them into the category with the highest possible score. For example, a patient with involvement of 2 large joints and 2 small joints is placed in the category "1–3 small joints," as this category has the higher score. Patients should be scored for their joint involvement assuming that all of the peripheral joints indicated above have been assessed. For the highest category of joint involvement, in which >10 joints must be involved (including at least 1 small joint), additional joints that can be considered for inclusion in this count include the temporomandibular joint, sternoclavicular joint, acromioclavicular joint, and others that may be reasonably expected to be involved in RA.

Definition of the serologic categories. ACPA and IgM-RF levels are usually reported in IU. Based on the upper limit of normal (ULN) for the respective laboratory test and assay the following definitions can be made: *negative* = less than or equal to the ULN for the laboratory test and assay; *low-level positive* = higher than the ULN but ≤ 3 times the ULN for the laboratory test and assay; *high-level positive* = >3 times the ULN for the laboratory test and assay. Where RF information is available only qualitatively or as a level, and thus positive or negative, patients with a positive level should be scored as "low-level positive" for RF. Where a value for a serologic test is not available *or* the normal range is not available for the reported test value, the result for that test should be considered "negative/normal." Patients should be scored only if information from at least 1 serologic test is available.

Definition of abnormal acute-phase response. The acute-phase response measures CRP or ESR are scored as normal or abnormal based on the local laboratory standards. If results of at least 1 of these 2 tests are abnormal, the patient should be scored as having an abnormal acute-phase response. If a value for an acute-phase reactant is not available *or* information on the normal range for the reported test value is not available, the result of that test should be considered "negative/normal." For ESR, a standard approach that considers age and sex differences would be valuable. Patients should be scored only if at least 1 acute-phase response test is available for scoring.

Definition of duration of symptoms. The "duration of symptoms" domain refers to the patient's self-report of the maximum duration of signs or symptoms of synovitis (pain, swelling, and tenderness) of any joint that is clinically involved at the time of assessment (i.e., the day the criteria are applied). Thus, joints that are reported to have been previously symptomatic but are not involved at the time of assessment, whether due to treatment or not, should not be considered in estimating symptom duration.

Discussion

We present here new classification criteria for rheumatoid arthritis, representing the culmination of an international collaborative effort supported by both a data-driven and a consensus-based approach. This classification scheme is designed to present a standardized approach to identifying that subset of individuals who present with an otherwise unexplained inflammatory arthritis of a peripheral joint(s), for whom the risk of symptom persistence or structural damage is sufficient to be considered for intervention with DMARDs. This is thus the new proposed paradigm for the entity "rheumatoid arthritis"—importantly, not criteria for "early" RA. If there was an intervention that was both infinitely effective and safe and could be provided at no cost and no discomfort, then there would be no requirement for such a subset to be identified, as every patient with inflammatory arthritis would be treated. Given that such an intervention does not exist, the search for appropriate classification rules is justified, and will also be helpful in guiding clinical diagnosis.

It is important, however, to stress that the criteria are meant to be applied only to eligible patients, in whom the presence of obvious *clinical* synovitis in at least 1 joint is central. They should not be applied to patients with mere arthralgia or to normal subjects. However, once definite clinical synovitis has been determined (or historical documentation of such has been obtained), as indicated in the glossary, a more liberal approach is allowed for determining number and distri-

bution of involved joints, which permits inclusion of tender or swollen joints.

Symmetry is not a feature of the new criteria since it did not carry an independent weight in any phase of the work. Inevitably, though, the greater the number of involved joints the higher the likelihood of bilateral involvement.

The development of these new criteria was based on diverse study cohorts and was performed by RA experts of diverse nationalities, enhancing the criteria set's generalizability. The final criteria also reflect consistency in domains of importance through use of 2 independent methodologies. Previous classification schemes centered on a pre-identified clinical concept, typified by the occurrence of a predominantly symmetric small joint polyarthritis associated with autoantibody production and a high prevalence of erosions (27). This was the "gold standard" used to devise the rules that could be applied in a repeatable manner to identify homogeneous groups for observation and study. The new criteria redefine RA, reflecting our collective hope that in the future, RA will no longer be characterized by erosive joint disease and persistence of symptoms, although these characteristics will continue to define established or longstanding untreated disease. This reflects several conceptual issues that are relevant in all areas of research and also in clinical practice.

Once the disease entity is redefined, existing epidemiologic data on prevalence will have less relevance. Generally, this should not be a major concern, since there are well-recognized difficulties in gathering and interpreting epidemiologic data regarding occurrence of RA: prevalence estimates are influenced by the effects of therapy and therefore are inherently unstable. The prevalence of RA could variously be described as the proportion of the population who have satisfied the new criteria at some relevant point in time.

The greater problem is the extrapolation of current literature on clinical trials and the design of future trials. The working group recommends that clinical trials should henceforth apply these new criteria; however, results from studies using the new criteria cannot necessarily be directly compared with the extensive body of existing work. In reality, in most trials, even of recent-onset RA, subjects with much higher levels of disease activity than is needed for fulfillment of the new criteria, and often those who have been treated unsuccessfully with multiple prior therapies, are selected (28). Thus, comparison between trials will be based much more on the distribution of disease activity at entry, for example, than the assumption that criteria satisfaction leads to homogeneity in patients recruited. Still, it might be useful, over this transition to the new criteria, for researchers to document the proportions of study subjects who fulfill the previous (1987) and the new RA classification criteria, to enable comparisons.

There is a potential problem related to the pursuit of basic research. For example, genetic association studies have relied on a standardized approach to phenotypic assessment based on the 1987 ACR criteria. Such association studies still hold and, as stated above, the new criteria are likely to be easily satisfied by the participants in such studies. RA is always considered a heterogeneous disorder, and the new criteria scheme will probably increase that heterogeneity. Thus, basic scientists should be aware and, where appropriate, restrict recruitment or stratify results based on clinically meaningful phenotypes. For example, even among patients fulfilling the 1987 criteria, those who are ACPA positive and those who are ACPA negative have been shown to differ from a pathogenetic, clinical, and prognostic perspective (29).

The criteria have been intentionally derived from paper patient cases and cohorts of newly presenting subjects with undifferentiated inflammatory synovitis. Once classified, unless an alternative explanation for the synovitis becomes apparent over time, the subject is labeled as having "definite RA." However, acknowledging that RA is not a static disease, the new criteria have been developed such that they can be applied to patients at more than one time point in the evolution of their symptoms and signs. Thus, a patient who does not fulfill criteria for definite RA at first presentation might be classified as having definite RA at a subsequent time point.

Rather than developing a parallel system for "established" disease or continuing to use the 1987 criteria for that purpose, the working group recommends that, when patient records allow, application of the criteria and assignment as definite RA may be made retrospectively. If there is a history compatible with definite RA as defined by these new criteria but no records of such, significant erosive disease seen on radiographs, typical of destructive RA, can be used as prima facie evidence of RA, precluding the need for applying additional criteria. Such individuals would need to be included as part of the total population of individuals affected by RA. It was not part of the working group's mission to define what is meant by significant erosive disease either in terms of the size, site, or number of erosions. Such agreement could be the task for further consensus, although current evidence sug-

gests that such a definition should be highly specific (30). Thus, future work will be needed to define what evidence of erosions is acceptable to be considered as "typical" of RA. This was a similar issue faced with the 1987 ACR criteria, but it did not detract from the usability of those criteria.

The use of the new criteria should be limited to a target population in whom there is otherwise no explanation (i.e., definite diagnosis) for their synovitis. The working group has deliberately not provided an exhaustive list of diagnoses or tests that should be performed to exclude these, since that is not the purpose of classification criteria. Differential diagnosis is a physician responsibility and will be influenced by patient age and sex, practice type, as well as variations in the background population in terms of the incidence of "competing" disorders. Thus, Lyme arthritis may be a frequent cause of synovitis in endemic areas, but testing for *Borrelia burgdorferi* would not be appropriate elsewhere. In this respect, the important utility of appropriate exclusion assessment is avoidance of misclassifying patients as having RA who might otherwise not need to be treated or have self-limiting disease.

It was not the charge of the working group to create a referral tool for primary care physicians. Indeed, the original 1987 ACR criteria were also not designed for such use. Primary care physicians and other specialists need an easy-to-use tool to facilitate identification of individuals who have an inflammatory arthritic syndrome and for whom referral to a rheumatologist for further evaluation and diagnosis is appropriate. Support for such an endeavor is already being undertaken as a joint effort by ACR/EULAR and other important stakeholders.

One limitation of the new criteria is that they are based on current knowledge. Genetic, proteomic, serologic, or imaging biomarkers that provide a more robust basis for risk stratification may emerge, and this would necessarily lead to a modification or amendment of the 2010 criteria. Similarly, biomarkers, including imaging modalities, that more robustly identify high-risk subgroups of patients with synovitis may one day be available and validated. A pertinent example of a new biomarker is ACPA (typically, with testing for anti-CCP). Based on a detailed literature review (31) and our analytical approach to physician decision-making, ACPA status did not add importantly to the ability to classify an individual as having RA, beyond the information provided by RF when it is positive. The working group has therefore included both markers (ACPA and RF) equally in the criteria. However, as ACPA testing becomes more standardized, further refinement may be needed.

Because there is no gold standard for a diagnosis of RA, the cutoff score of ≥ 6 is the best estimate from the current approaches used; testing in other cohorts will provide further evidence regarding its validity. Since the classification scheme actually provides a continuum of "risk for developing persistent and/or erosive RA" (i.e., it assigns the risk or probability of developing RA on a continuous score (from 0 to 100%), there is scope for investigators to use other cut points—or multiple cut points—for different purposes. For example, in a clinical trial of a new potentially toxic agent, a higher, more conservative, cut point might be more appropriate; this is akin to clinical trials enrolling patients who meet criteria but also have evidence of a certain degree of severity or extent of involvement. In contrast, a population study of familial aggregation might use a less restrictive cut point. As such, there is information derived from scores across the range from 0 to 10 that may be utilized for different purposes in the future.

The working group has deliberately labeled these criteria as "classification criteria" as opposed to "diagnostic criteria." The aim is to provide a standardized approach for discriminating, from a population of individuals presenting with undifferentiated synovitis, the subgroup with the highest probability of persistent or erosive RA, who may be enrolled into clinical trials and other studies through the use of uniform criteria. These individuals are also the ones who may therefore benefit from DMARD intervention. The criteria do not remove the onus on individual physicians, especially in the face of unusual presentations, to reach a diagnostic opinion that might be at variance from the assignment obtained using the criteria. Nonetheless, it is recognized that the new criteria will likely also be used as a diagnostic aid and be required to be satisfied, for example, by health care providers to enable access to particular interventions. However, much like other classification criteria, clinicians may be able to diagnose an individual who has not met the classification criteria definition or who has features that are not a component of the classification criteria. Diseases often present a much wider spectrum in clinical medicine that can be expected to be captured by classification criteria, the purpose of which is simply to provide a uniform set of standards by which an individual can be classified as having a clinical entity or not.

The new criteria need to be tested in several clinical situations and settings. Physicians need to report particularly if there is an important proportion of newly

presenting patients who do not satisfy these criteria but for whom there is a compelling reason to treat with a DMARD, or who on followup, *without* a change in their classification status develop persistent or erosive disease. Validation in 3 of the cohorts available to us showed that the criteria were satisfied in 87–97% of the patients in whom the physicians chose to initiate MTX treatment.

In summary, the new ACR/EULAR classification criteria for RA present a new approach with a specific emphasis on identifying patients with a relatively short duration of symptoms who may benefit from early institution of DMARD therapy or entry into clinical trials of promising new agents that may halt the development of disease that currently fulfills the 1987 ACR criteria.

ACKNOWLEDGMENTS

We are grateful to Celina Alves, Carly Cheng, Tracey Farragher, Elisabeth Hensor, Jolanda Luime, Klaus Machold, Maria Dahl Mjaavatten, Valerie Nell, Nathalie Rincheval, Marleen van de Sande, and Annette van der Helm-van Mil, who were involved in the development, data management, or maintenance of their respective data sets used in Phase 1 of the project, and to Rohit Aggarwal, Dinesh Khanna, Katherine Liao, Raj Nair, and Sarah Ringold, who were involved in the design or implementation of Phase 2. We also wish to thank the ACR and the EULAR for their financial support of this project. We are especially grateful to Amy Miller and Regina Parker from the ACR and Heinz Marchesi and Anja Schönbächler from the EULAR, for their administrative support of the project.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Silman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Aletaha, Neogi, Silman, Felson, Birnbaum, Bykerk, Combe, Costenbader, Dougados, Emery, Hazes, Huizinga, Kay, Kvien, Moreland, Naden, Smolen, Stanislawska-Biernat, Vencovský, Hawker.

Acquisition of data. Aletaha, Neogi, Silman, Bingham, Birnbaum, Burmester, Bykerk, Combe, Costenbader, Dougados, Emery, Hazes, Huizinga, Kavanaugh, Kay, Kvien, Laing, Ménard, Naden, Smolen, Stanislawska-Biernat, Tak, Upchurch, Vencovský, Hawker.

Analysis and interpretation of data. Aletaha, Neogi, Silman, Funovits, Bingham, Birnbaum, Burmester, Bykerk, Cohen, Combe, Dougados, Emery, Ferraccioli, Hazes, Hobbs, Huizinga, Kay, Laing, Mease, Ménard, Moreland, Naden, Pincus, Smolen, Stanislawska-Biernat, Symmons, Tak, Upchurch, Vencovský, Wolfe, Hawker.

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Arthritis Care & Research
DOI 10.1002/acr.22783
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SPECIAL ARTICLE

2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

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This article is published simultaneously in *Arthritis & Rheumatology*.

The views expressed herein are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States Government.

Supported by the American College of Rheumatology.

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Dr. Singh has received consulting fees, speaking fees, and/or honoraria from Savient, Allergan, Regeneron, Merz, Iroko, and Bioiberica (less than $10,000 each) and from Takeda and Dinora (more than $10,000 each), and has received grant/research support from Horizon. Dr. Saag has received consulting fees, speaking fees, and/or honoraria from Abbott, Amgen, Bayer, Bristol-Myers Squibb, Lilly, Merck, Pfizer, and Roche/Genentech (less than $10,000 each) and from Ardea/AstraZeneca (more than $10,000). Dr. Curtis has received con-

Objective. **To develop a new evidence-based, pharmacologic treatment guideline for rheumatoid arthritis (RA).**
Methods. **We conducted systematic reviews to synthesize the evidence for the benefits and harms of various treatment options. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence. We employed a group consensus process to grade the strength of recommendations (either strong or conditional). A strong recommendation indicates that clinicians are certain that the benefits of an intervention far outweigh the harms (or vice versa). A conditional recommendation denotes uncertainty over the balance of benefits and harms and/or more significant variability in patient values and preferences.**
Results. **The guideline covers the use of traditional disease-modifying antirheumatic drugs (DMARDs), biologic agents, tofacitinib, and glucocorticoids in early (<6 months) and established (≥6 months) RA. In addition, it provides recommendations on using a treat-to-target approach, tapering and discontinuing medications, and the use of biologic agents and DMARDs in patients with hepatitis, congestive heart failure, malignancy, and serious infections. The guideline addresses the use of vaccines in patients starting/receiving DMARDs or biologic agents, screening for tuberculosis in patients starting/receiving biologic agents or tofacitinib, and laboratory monitoring for traditional DMARDs. The guideline includes 74 recommendations: 23% are strong and 77% are conditional.**
Conclusion. **This RA guideline should serve as a tool for clinicians and patients (our two target audiences) for pharmacologic treatment decisions in commonly encountered clinical situations. These recommendations are not prescriptive, and the treatment decisions should be made by physicians and patients through a shared decision-making process taking into account patients' values, preferences, and comorbidities. These recommendations should not be used to limit or deny access to therapies.**

INTRODUCTION

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults (1). RA has a significant negative impact on the ability to perform daily activities, including work and household tasks, and health-related quality of life, and it increases mortality (2–4). The American College of Rheumatology (ACR) last published a guideline for RA management in 2012 (5), which was an update of the 2008 RA guideline (6).

Because there has been rapid accrual of evidence and new therapies, advancement of guideline development methodologies, and the need to broaden the scope of its 2012 RA recommendations, the ACR has developed a new 2015 RA pharmacologic treatment guideline. This guideline addresses 6 major topics: 1) use of traditional disease-modifying antirheumatic drugs (traditional/conventional DMARDs, herein referred to as DMARDs), biologic DMARDs (herein referred to as biologics), and tofacitinib, including tapering and discontinuing medications, and a treat-to-target approach; 2) use of glucocorticoids; 3) use of biologics and DMARDs in high-risk populations (i.e., those with hepatitis, congestive heart failure, malignancy, and serious infections); 4) use of vaccines in patients starting/receiving DMARDs or biologics; 5) screening for tuberculosis (TB) in the context of biologics or tofacitinib; and 6) laboratory monitoring for traditional DMARDs.

METHODS

Overall methodology. We developed this guideline following the recently revised ACR guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process includes the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (available at www.gradeworkinggroup.org) (7–9).

Teams involved. A Core Leadership Team (see Appendix A for a list of Panel and Team members) supervised the project and was responsible for defining the project scope, drafting the clinical questions to be addressed by the guideline, coordinating with the Literature Review Team's efforts, and drafting the manuscript based on vot-

sulting fees, speaking fees, and/or honoraria from Pfizer, Bristol-Myers Squibb, Crescendo, and AbbVie (less than $10,000 each) and from Roche/Genentech, UCB, Janssen, the Consortium of Rheumatology Researchers of North America (CORRONA) registry, and Amgen (more than $10,000 each). Dr. Furst has received consulting fees, speaking fees, and/or honoraria from AbbVie, Actelion, Amgen, Bristol Myers Squibb, Cytori, Janssen, Gilead, GlaxoSmithKline, Novartis, Pfizer, Roche/Genentech, and UCB (less than $10,000 each) and has received research support from AbbVie, Actelion, Amgen, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Novartis, Pfizer, Roche/Genentech, and UCB. Dr. Kavanaugh has received consulting fees, speaking fees, and/or honoraria from Amgen, AbbVie, and Pfizer (less than $10,000 each) and grant/research support from Amgen, AbbVie, Bristol-Myers Squibb, Janssen, UCB, Roche, and Pfizer. Dr. O'Dell has received consulting fees, speaking fees, and/or honoraria from Medac, Antaes, AbbVie, Bristol-Myers Squibb, and Lilly (less than $10,000 each). Dr. King receives indirect sponsor payments as Medical Director of the North Mississippi Arthritis and Research Center. Ms Leong has received consulting fees, speaking fees, and/or honoraria from Horizon, GlaxoSmith-Kline, and Zimmer (less than $10,000 each). Dr. Matteson receives royalties from UpToDate, and has received grant/research support from Roche, Genentech, Mesoblast, Ardea, Novartis, Sanofi, Centocor, Janssen, Celgene, UCB, and GlaxoSmithKline. Dr. Grober has received consulting fees, speaking fees, and/or honoraria from Medac (less than $10,000). Dr. St.Clair owns stock or stock options from Bristol-Myers Squibb, Merck, and Proctor & Gamble, receives royalties from UpToDate, and has received grant/research support from Biogen. Dr. McAlindon has received consulting fees, speaking fees, and/or honoraria from Sanofi-Aventis, Samumed, Fidia, Flexion, and McNeil Consumer Healthcare (less than $10,000 each) and has a patent on an online clinical trial methodology through Boston University Medical School.

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Submitted for publication March 19, 2015; accepted in revised form October 14, 2015.

ing by a panel (described below). The Core Leadership Team was led by a chair (JAS) who possessed both content and methodologic expertise. The Core Leadership Team also included a methodologist (EAA), who advised on the process and provided input on the GRADE summary of findings tables (see Evidence Report as part of Supplementary Appendix 1 available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22783/abstract), and experts in guideline development. A Literature Review Team (see Appendix A for a list of Panel and Team members) conducted the literature review, graded the quality of evidence, developed the summary of findings tables, and produced an evidence report. A Content Panel, composed of 4 content experts (see Appendix A for a list of Panel and Team members) reviewed and provided feedback on the clinical questions and the evidence report, and provided consultation throughout the project. Finally, a Voting Panel (see Appendix A for a list of Panel and Team members) helped determine which clinical questions would be asked and which outcomes were critical, and they voted on the final recommendations after reviewing the evidence provided by the Literature Review Team. The Voting Panel included rheumatologists with expertise and clinical experience in treating RA (AK, JOD, CK, ELM, JTS, BD, JG, EWSC, ET), as well as 2 patient representatives (AL, SG). Training was conducted with all members of the guideline development group to prepare them for their roles, including specific sessions on the ACR guideline process and GRADE methodology.

Disclosures and management of conflicts of interest. In accordance with ACR policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) disclosed all relationships in writing at the beginning, middle, and end of the project. Disclosures were compared against a previously drafted list of "affected companies" (i.e., companies or organizations that were considered reasonably likely to be positively or negatively affected by care delivered in accordance with the guideline) to determine which relationships were considered conflicts of interest for purposes of this project. Individuals whose primary employment (>51% of work time/effort) was with a company that manufactured or sold therapeutics or diagnostics were not eligible to participate.

The project Principal Investigator (JAS) and Literature Review Team Leader (TM) had no relevant conflicts of interest for the full 12 months before this project began, and a majority (>51%) of all guideline development team members, including the Principal Investigator and Literature Review Team Leader, had no relevant conflicts of interest for the duration of the project. A participant who had any relationship with an affected company was counted as conflicted (i.e., toward the allowed threshold) regardless of the type or subject of the relationship. Intellectual conflicts, such as a prior publication or presentation on an RA therapeutic, were recognized as important and were required to be disclosed, but because they were ubiquitous, participants with intellectual conflicts were not counted as conflicted (i.e., toward the allowed threshold) based on their intellectual conflict alone.

Participant disclosures were included in the project plan that was posted online for public comment (see description below). In addition, disclosures of all participants were shared with each project participant in writing. At the face-to-face Voting Panel meeting, verbal disclosures were provided before any content discussion. Updated participant disclosures, as well as ACR committee reviewer disclosures, are available online (www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Rheumatoid-Arthritis). Author disclosures are detailed in the footnotes of this article.

Scope and target audience. The Core Leadership Team decided that the guideline would address topics concerning the treatment of RA and not address any topics related to diagnosis, monitoring of disease activity, surgical interventions, or physical therapy interventions. The target audience includes both clinicians and their patients with RA. The ACR plans to develop derivative products in the future, including a pocket card, an app version of this guideline, and a patient education tool to facilitate implementation.

Establishing key principles and PICO (population, intervention, comparator, and outcomes) development. Key principles and provisos, key terms, descriptions, and drug categories used in the guideline development process are shown in Table 1. These key principles were first reviewed by the Content Panel and the Core Leadership Team. The key principles were then provided to the Voting Panel when they reviewed the drafted evidence report, and also when they discussed and voted on each recommendation. The Core Leadership Team collaborated with the Content Panel to develop the initial set of PICO-formatted clinical questions for the guideline (10). We considered clinically relevant interventions and comparators after extensive discussion with the Content Panel and the Core Leadership Team, balancing comprehensiveness with feasibility. These PICO questions were posted for 30 days on the ACR web site for public comment, and revised accordingly. The final set of PICO questions addressed the 6 major topics listed above.

Systematic synthesis of the literature. *Literature searches.* We performed systematic searches of the published literature to identify relevant evidence for the PICO questions (11). Study designs in the literature review included systematic reviews, randomized controlled trials (RCTs), and observational studies (including case series). We searched OVID Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; Cochrane Central Register of Controlled Trials; and Health Technology Assessments) (see Supplementary Appendix 2 available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22783/abstract) (11). The searches were performed using database-specific subject headings and keywords related to the following domains of interest: RA, traditional/conventional DMARDs, tumor necrosis factor inhibitor (TNFi) biologics (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab), non-TNF biologics (abatacept, rituximab, or tocilizumab), tofacitinib, glucocorticoids, and adverse events. We limited our searches to adults ages

Table 1. Key provisos and principles, key terms, definitions, and drug categories for the 2015 ACR recommendations for the treatment of rheumatoid arthritis*

Key provisos and principles

1. Focus on common clinical scenarios, not exceptional cases.
2. Cost is a consideration in these recommendations; however, explicit cost-effectiveness analyses were not conducted.
3. Disease activity measurement using an ACR-recommended measure should be performed in a majority of encounters for RA patients (16).†
4. Functional status assessment using a standardized, validated measure should be performed routinely for RA patients, at least once per year, but more frequently if disease is active. Examples of commonly used functional status measures include Health Assessment Questionnaire, Health Assessment Questionnaire II, Multidimensional Health Assessment Questionnaire, PROMIS (available at https://www.assessmentcenter.net/) Physical Function 10-item, PROMIS Physical Function 20-item, and PROMIS Physical Function Computerized Adaptive Tests (PROPFCAT).
5. If a patient has low RA disease activity or is in clinical remission, switching from one therapy to another should be considered only at the discretion of the treating physician in consultation with the patient. *Arbitrary switching between RA therapies based only on a payer/insurance company policy is not recommended*.
6. A treatment recommendation favoring one medication over another means that the preferred medication would be the recommended first option. However, favoring one medication over the other does not imply that the nonfavored medication is contraindicated for use in that situation; it may still be a potential option under certain conditions.

Key terms	Definitions
Adult RA patient	Adults, ≥18 years, meeting the ACR RA classification criteria (1987 or 2010 revised criteria) (81,82).
Health benefits and harms	Efficacy and safety of treatments including desirable and undesirable effects.
Early RA	RA with duration of disease/symptoms of <6 months, where "duration" denotes the length of time the patient has had symptoms/disease, not the length of time since RA diagnosis.
Established RA	RA with duration of disease/symptoms of ≥6 months or meeting 1987 ACR RA classification criteria (81).‡
Disease activity	Categorized as low, moderate, or high as per validated scales (Table 2) (144–150). Moderate and high disease activity categories were combined based on feedback from the Content Panel, as used previously for the 2012 ACR RA treatment recommendations.
RA remission	A joint ACR/EULAR task force defined remission as a tender joint count, swollen joint count, C-reactive protein level (mg/dl), and patient global assessment of ≤1 each or a Simplified DAS of ≤3.3 (151), 1 of 6 ACR-endorsed disease activity measures.†
Optimal dosing of RA treatments	1) Dosing to achieve a therapeutic target derived from mutual patient-clinician consideration of patient priorities, and 2) given for at least 3 months before therapy escalation or switching.
DMARD failure	Failure of traditional/conventional DMARD(s) due to lack of efficacy/desired response or side effects.
Biologic failure	Failure of biologic(s) due to lack of efficacy/desired response or side effects.
Secondary biologic failure	Biologic was efficacious initially but subsequently became inefficacious.
Active hepatitis B infection	Hepatitis B surface antigen positive, hepatitis B surface antibody negative, hepatitis B core antibody total positive (less important), AST/ALT typically increased, HBV DNA positive (if checked).
Hepatitis C infection	HCV antibody positive, HCV RNA positive, AST/ALT typically increased.
NYHA class III and IV	NYHA class III includes patients with cardiac disease resulting in marked limitation of physical activity with less than ordinary physical activity causing fatigue, palpitation, dyspnea, or angina, but no symptoms at rest. NYHA class IV includes patients with cardiac disease resulting in inability to carry on any physical activity without discomfort, symptoms of heart failure are present even at rest, and discomfort increases if any physical activity is undertaken (152).

Drug category	Descriptions
Methotrexate	Used either oral or subcutaneous (a DMARD).
DMARDs§	Traditional/conventional DMARDs including HCQ, LEF, MTX, or SSZ (excludes azathioprine, cyclosporine, minocycline and gold), it does not include tofacitinib, which is considered separately.¶
DMARD monotherapy	Most often defined as the use of MTX monotherapy, but may also be SSZ, HCQ, or LEF.
Double DMARD therapy	MTX+SSZ, MTX+HCQ, SSZ+HCQ, or combinations with LEF.

(continued)

Table 1. *(Cont'd)*

Drug category	Descriptions
Triple DMARD therapy	MTX+SSZ+HCQ.
DMARD combination therapy	Double or triple traditional/conventional DMARD therapy.
Tofacitinib	Oral synthetic small molecule.
Biologics	TNFi biologic or non-TNF biologic (excludes anakinra).§
TNFi biologics	Adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab.
Non-TNF biologics	Abatacept, rituximab, or tocilizumab (excludes anakinra).§
Low-dose glucocorticoid	≤10 mg/day of prednisone (or equivalent).
High-dose glucocorticoid	>10 mg/day of prednisone (or equivalent) and up to 60 mg/day with a rapid taper.#
Short-term glucocorticoid	<3 month treatment.

* ACR = American College of Rheumatology; RA = rheumatoid arthritis; PROMIS = Patient-Reported Outcomes Measurement Information System; EULAR = European League Against Rheumatism; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; AST = aspartate aminotransferase; ALT = alanine aminotransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; NYHA = New York Heart Association; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; SSZ = sulfasalazine; TNFi = tumor necrosis factor inhibitor; COBRA = Combinatietherapie Bij Reumatoide Artritis.
† Any of the ACR recommended disease activity measures may be chosen, as described in ref. 16.
‡ New classification criteria for RA (ACR/EULAR collaborative initiative) were published in 2010 (82), the definition of established RA is based on the 1987 ACR RA classification criteria, since the 2010 ACR RA classification allows a much earlier diagnosis.
§ Anakinra was considered but not included in these guidelines due to its infrequent use in RA and lack of new data since 2012.
¶ Azathioprine, cyclosporine, minocycline and gold were considered but not included in these guidelines due to their infrequent use in RA and/or lack of new data since 2012.
# Regimen based on that described in the COBRA study (153).

≥18 years and to English language publications. Duplicate references were removed. We excluded narrative reviews, editorials, scientific conference abstracts, and case reports.

The literature related to treatment modalities covered by past ACR RA guidelines (i.e., traditional/conventional DMARDs, TNFi and non-TNF biologics) and tofacitinib was searched to include articles published from January 1, 2009 through March 3, 2014. For other treatment modalities not covered by past ACR RA guidelines (i.e., glucocorticoids), we searched the databases from inception until March 3, 2014. We updated initial literature searches on September 17, 2014. All searches were developed by a medical librarian in collaboration with the Literature Review Team and were peer reviewed by a second medical librarian.

Study selection. The literature search results underwent primary screening in DistillerSR software (Evidence Partners). During primary literature screening, 2 reviewers (various pairs, made from a pool of reviewers including authors MCS, EV, CM, and MO, as well as the medical librarian) independently reviewed the title and abstract of each article for potential eligibility. A third reviewer (RRB) resolved conflicts regarding inclusion versus exclusion. Articles judged as potentially eligible were tagged for electronic matching to specific PICO questions, and subsequently underwent full-text article screening. Each full text was screened by 2 reviewers and independently tagged with PICO-matching criteria. A secondary hand sorting of all randomized studies was conducted to ensure successful matching of relevant evidence to PICO questions (for details on the study selection see Supplementary Appendix 3 available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22783/abstract).

Data extraction and analysis. We extracted study data for each PICO question into RevMan software (12). When determining which data to include, we followed the GRADE methodology that gives preference to RCTs over observational studies as the highest-quality source of evidence. Whenever data from both randomized and observational trials were available, and the RCT was of high quality, we extracted RCT data only (13). A RevMan file was created for each PICO question, and data were pooled and analyzed using this software. Continuous outcome variables were analyzed using the inverse variance method in a random effects model. Continuous outcomes were reported as mean differences with 95% confidence intervals; standardized mean differences (similar in concept to effect sizes) were used when the outcome was measured with different scales. Dichotomous variables were analyzed using the Mantel-Haenszel method in a random effects model. These variables were reported as risk ratios with 95% confidence intervals.

Quality assessment and evidence report formulation. We exported RevMan analyses into GRADEpro software to formulate a GRADE summary of findings table for each PICO question. The quality of evidence, such as the confidence in the effect estimates for each outcome, was evaluated based on GRADE quality assessment criteria. Two independent reviewers (RRB, MCS) performed this GRADE quality assessment in duplicate and discordance was resolved by consensus. This included the risk of bias in included trials, the likelihood of publication bias, inconsistency between trial results, indirectness of the evidence (e.g., differences between populations, interventions, or outcomes of interest in the group to whom the recommendation applies versus those who were included in the studies referenced), and imprecision (wide confidence intervals, usually due to a small number of patients or events, or those situations where clinical decision-making would differ at the extremes of the confidence interval).

The GRADE method distinguishes 4 levels of quality of evidence based on the degree of confidence that the pooled effect estimate lies close to the true effect. Thus, the quality of evidence for each outcome could be rated as high, moderate, low, or very low. The overall evidence quality grade was the lowest quality rating among the individual outcomes deemed

	Strong recommendation	*Conditional recommendation*
Patients	**Most people in your situation would want the recommended course of action and only a small proportion would not**	*The majority of people in your situation would want the recommended course of action, but many would not**
Clinicians	**Most patients should receive the recommended course of action**	*Be prepared to help patients to make a decision that is consistent with their own values*
Policy makers	**The recommendation can be adapted as a policy in most situations**	*There is a need for substantial debate and involvement of stakeholders*

Figure 1. Implications of strong and conditional GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology recommendations (154). * = majority means >50% of the people.

critical for the comparison between interventions (14). In the absence of any data, the level of evidence was rated as very low, because it was based on clinical experience only.

We compiled the resulting summary of findings tables in an evidence report (see Supplementary Appendix 1, http://onlinelibrary.wiley.com/doi/10.1002/acr.22783/abstract) that was accompanied by a qualitative summary of the evidence for each PICO question. The Content Panel reviewed the drafted evidence report and revised the report to address evidence gaps prior to presentation to the Voting Panel. We referred to other society/organization guidelines for topics that do not exclusively relate to rheumatologic care, such as liver disease (American Association for the Study of Liver Diseases [AASLD]) and TB screening and immunization (Centers for Disease Control and Prevention [CDC]).

Moving from evidence to recommendations. Each recommendation was made based on a consideration of the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the effect estimates), and patients' values and preferences, as per GRADE methodology.

A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention far outweigh the harms (or vice versa) (7–9) (Figure 1). A conditional recommendation denotes uncertainty over the balance of benefits and harms, such as when the evidence quality is low or very low, or when patient preferences or costs are expected to impact the decision. Thus, conditional recommendations refer to decisions where incorporation of patient preferences is an essential element of decision making.

Consensus building. The Voting Panel received the evidence report for review before it met to discuss and decide on the final recommendations. For each PICO question, the Voting Panel heard an oral summary of the evidence and provided votes on the direction and strength of the related recommendation during a face-to-face meeting held on October 5–6, 2014, and subsequent conference calls and e-mails. The voting process was anonymous and conducted using Poll Everywhere software (available at www.polleverywhere.com). We used the 70% consensus threshold, which has been used previously in other similar processes (15) and in previous ACR guidelines (5,6). If 70% consensus was not achieved during an initial vote, the panel members held additional discussions before voting again. In some instances (specifically, DMARD monotherapy failure in early and established RA, hepatitis B, hepatitis C, and previously treated/untreated solid organ cancer), the Voting Panel decided, based on its review of the evidence and its round 1 votes, to combine certain treatment options. They then voted on a new recommendation statement that covered a group of treatment options instead of considering each question separately. In addition, the Voting Panel dropped a number of PICO questions because the clinical scenario was uncommon, irrelevant, or redundant (see Supplementary Appendix 4 available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22783/abstract).

The GRADE methodology contributed a great deal of transparency to the voting process. For example, all of the evidence tables contained detailed descriptions of the criteria upon which the evidence quality was rated (such as estimates of risk of bias or indirectness). As allowed for in GRADE, in some instances, the Voting Panel chose to provide a recommendation in disagreement with the expected strength based on the overall evidence quality (i.e., a strong recommendation despite a low quality rating of evidence). In such cases, a written explanation was provided describing the reasons behind this decision.

Final review and approval of the manuscript by the ACR. In addition to journal peer review, the manuscript was reviewed by the ACR Guideline Subcommittee, ACR Quality of Care Committee, and the ACR Board of Directors, a process that involved over 40 reviewers (details available at www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Rheumatoid-Arthritis). These ACR oversight groups did not mandate that certain recommendations be made within the guideline, but rather, these ACR committees served as peer reviewers.

RESULTS/RECOMMENDATIONS

An abbreviated guideline summary of recommendations for patients with early RA, established RA, and high-risk comorbidities is available (see Executive Summary, Supplementary Appendix 5, available on the *Arthritis*

Table 2. Instruments to measure rheumatoid arthritis disease activity and to define remission*

Instrument (reference)	Thresholds of disease activity
Patient Activity Scale (PAS) or PASII (range 0–10) (149)	Remission: 0–0.25 Low activity: >0.25–3.7 Moderate activity: >3.7 to <8.0 High activity: ≥8.0
Routine Assessment of Patient Index Data 3 (RAPID3) (range 0–10) (155)	Remission: 0–1.0 Low activity: >1.0–2.0 Moderate activity: >2.0–4.0 High activity: >4.0–10
Clinical Disease Activity Index (CDAI) (range 0–76.0) (156)	Remission: ≤2.8 Low activity: >2.8–10.0 Moderate activity: >10.0–22.0 High activity: >22
Disease Activity Score (DAS) 28 erythrocyte sedimentation rate (ESR) (range 0–9.4) (157)	Remission: <2.6 Low activity: ≥2.6 to <3.2 Moderate activity: ≥3.2 to ≤5.1 High activity: >5.1
Simplified Disease Activity Index (SDAI) (range 0–86.0) (158)	Remission: ≤3.3 Low activity: >3.3 to ≤11.0 Moderate activity: >11.0 to ≤26 High activity: >26

* These 6 measures were endorsed by the American College of Rheumatology in 2012 (16). Other measures are now available to clinicians, but they were not included in this guideline because it was beyond the scope of this review. Adapted from ref. 16.

Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22783/abstract).

How to interpret the recommendations

1. Strong recommendations are highlighted in green and bolded, and conditional recommendations are highlighted in yellow and italicized in the figures (Figure 1). A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. A conditional recommendation means that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach.
2. In general, treatment choices are listed in the same order throughout the document (traditional DMARDs, TNFi, non-TNF, tofacitinib), and then alphabetically within each category. When more than one treatment is included as an option, the order does not imply any hierarchy, i.e., each of the treatment options (A or B or C) is recommended equally.

   For each recommendation, details regarding the supportive evidence or conditions (for conditional recommendations, but sometimes also for strong recommendations) are summarized in a section titled "Reasoning underlying the recommendations . . ." For example, conditions that the panel considered included comorbidities, patient perception of burden of taking medications, side-effect profile, and cost. Additional details including PICO questions and the GRADE evidence tables are available in Supplementary Appendix 1, http://onlinelibrary.wiley.com/doi/10.1002/acr.22783/abstract).
3. The Voting Panel members agreed to key principles and provisos, key terms, and descriptions prior to voting on the 2015 ACR RA treatment recommendations. These are explicitly stated in Table 1 and apply to the entire guideline. RA disease activity was defined as low, moderate, or high, as previously described (16) (Table 2).

Recommendations for the treatment of patients with early RA

Recommendations for treatment of early RA (disease duration <6 months) patients are provided in Figures 2 and 3. An executive summary of these recommendations is available in Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/acr.22783/abstract.

Reasoning underlying the recommendations for the treatment of early RA. To achieve the above recommendations (Figure 2), the panel discussed several different PICO questions for early RA. The reasoning underlying the recommendations is described below.

PICO A.1. Despite the low quality evidence, the recommendation is **strong** because the Voting Panel concluded that the improved outcomes experienced by patients with established RA using a tar-

Recommendations for patients with symptomatic Early RA	Level of Evidence (evidence reviewed)
1. Regardless of disease activity level, use a treat-to-target strategy rather than a non-targeted approach (PICO A.1).	**Low (17)**
2. If the disease activity is low, in patients who have never taken a DMARD: **• use DMARD monotherapy (MTX preferred) over double therapy (PICO A.2).** **• use DMARD monotherapy (MTX preferred) over triple therapy (PICO A.3).**	**Low (18-21)** **Low (22-25)**
3. If the disease activity is moderate or high, in patients who have never taken a DMARD: *• use DMARD monotherapy over double therapy (PICO A.4).* *• use DMARD monotherapy over triple therapy (PICO A.5).*	*Moderate (18,20,21)* *High (22-25)*
4. If disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARDs or a TNFi or a non-TNF biologic (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (PICO A.7).	**Low (26-28)**
5. If disease activity remains moderate or high despite DMARDs: *• use a TNFi monotherapy over tofacitinib monotherapy (PICO A.8).* *• use a TNFi + MTX over tofacitinib + MTX (PICO A.9).*	*Low (29)* *Low (30)*
6. If disease activity remains moderate or high despite DMARD (PICO A.6) or biologic therapies (PICO A.12), add low-dose glucocorticoids.	*Moderate (31-37)* *Low (31-37)*
7. If disease flares, add short-term glucocorticoids at the lowest possible dose and for the shortest possible duration (PICO A.10, A.11).	*Very low (38-43)*

Figure 2. Summary of 2015 American College of Rheumatology recommendations for the treatment of Early rheumatoid arthritis (RA). Green and bolded = strong recommendation. A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. Yellow and italicized = conditional recommendation: The desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. A treatment recommendation favoring one medication over another means that the preferred medication would be the recommended first option and the nonpreferred medication may be the second option. Favoring one medication over the other does not imply that the nonfavored medication is contraindicated for use; it is still an option. Therapies are listed alphabetically; azathioprine, gold, and cyclosporine were considered but not included. Disease-modifying antirheumatic drugs (DMARDs) include hydroxychloroquine, leflunomide, methotrexate (MTX), and sulfasalazine. PICO = population, intervention, comparator, and outcomes; TNFi = tumor necrosis factor inhibitor. For definitions and descriptions, see Table 1.

geted approach should be generalizable to those with early RA (Figure 2).

PICOs A.2 and A.3. Despite the low quality evidence, the recommendation is **strong** because 1) there is no evidence in favor of triple therapy in this setting, 2) DMARD monotherapy is generally more acceptable (i.e., easier to take, less cost to the patient) to early RA patients with low disease activity than DMARD combination regimens, and 3) DMARD monotherapy is generally better tolerated than combination DMARD therapy. The panel also voted that methotrexate (MTX) should be the preferred initial DMARD for most early RA patients.

PICOs A.4 and A.5. The recommendation is *conditional* because 1) the evidence is of low quality and the evidence for differences in side effects is imprecise, 2) there is little difference in the benefit of double DMARD therapy over monotherapy, and 3) triple therapy might be preferred by some patients who desire a more rapid short-term benefit (e.g., earlier resumption of work activities) and are willing to assume potential added risk.

PICOs A.6 and A.12. The recommendation is *conditional* because 1) the evidence is of low quality, and 2) although glucocorticoid therapy is effective as a short-term (i.e., less than 3 months) therapy to "bridge" patients until realizing the benefits of DMARDs, this decision must be balanced by the lack of long-term glucocorticoid safety studies. The risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and the duration of therapy is short.

PICO A.7. The recommendation is **strong** despite the low quality of evidence because, for a patient failing DMARD monotherapy, clinical experience and indirect evidence support the benefits of adding these treatment options, and recommending no additional treatment is not an option. When deciding which therapy to use, considerations may include cost, comorbidities, burden of taking medications (i.e., 1 versus multiple, oral versus other routes) and side-effect profile. The panel also voted that biologic therapy should

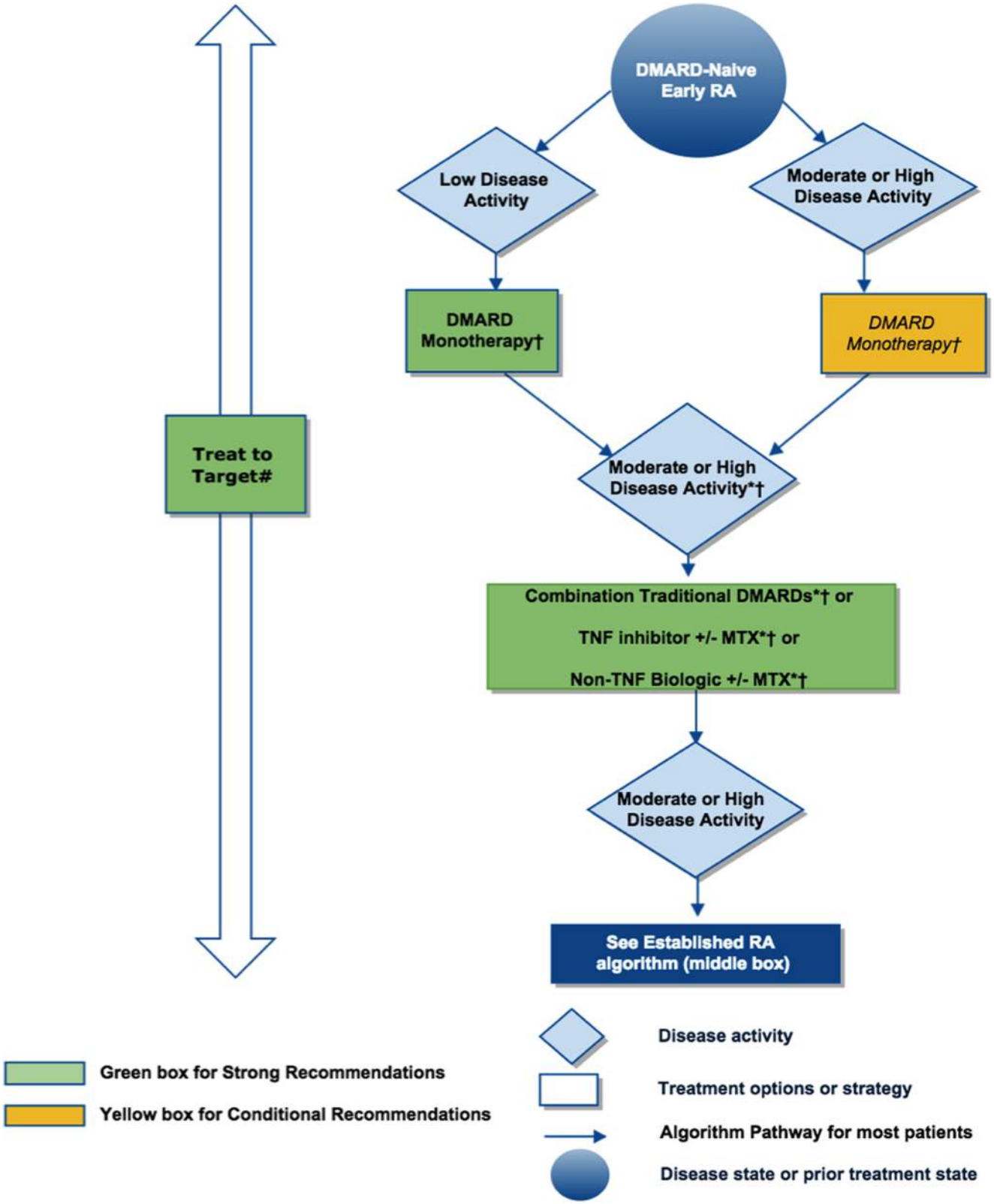
DMARD-Naive Early RA
Low Disease Activity
Moderate or High Disease Activity
DMARD Monotherapy†
DMARD Monotherapy†
Treat to Target#
Moderate or High Disease Activity*†
Combination Traditional DMARDs*† or
TNF inhibitor +/- MTX*† or
Non-TNF Biologic +/- MTX*†
Moderate or High Disease Activity
See Established RA algorithm (middle box)
Green box for Strong Recommendations
Yellow box for Conditional Recommendations
Disease activity
Treatment options or strategy
Algorithm Pathway for most patients
Disease state or prior treatment state

Figure 3. 2015 American College of Rheumatology recommendations for the treatment of Early rheumatoid arthritis (RA), defined as disease duration <6 months. * = consider adding low-dose glucocorticoids (≤10 mg/day of prednisone or equivalent) in patients with moderate or high RA disease activity when starting disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure. † = also consider using short-term glucocorticoids (defined as <3 months treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible duration to provide the best benefit-risk ratio for the patient. # = treatment target should ideally be low disease activity or remission. For the level of evidence supporting each recommendation, see the related section in the Results. This figure is derived from recommendations based on PICO (population, intervention, comparator, and outcomes) questions A.1 to A.12. For definitions of disease activity (categorized as low, moderate, or high) and descriptions, see Tables 1 and 2. MTX = methotrexate.

be used in combination with MTX, when possible, due to superior efficacy of this combination over biologic monotherapy.

PICOs A.8 and A.9. The recommendation is *conditional* because 1) the evidence is low quality, and 2) there are potential longer-term safety concerns related to tofacitinib that need more study, partly related to the shorter experience using tofacitinib.

PICOs A.10 and A.11. The recommendation is *conditional* because the evidence is of low quality because it is indirect, and the risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and duration of therapy is short.

Recommendations for the treatment of patients with established RA

Recommendations for treatment of established RA patients (disease duration ≥6 months), including tapering therapy, are provided in Figures 4 and 5. An executive summary of these recommendations is available in Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/acr.22783/abstract.

Reasoning underlying the recommendations for the treatment of established RA

PICO B.1. The recommendation is **strong** because, based on moderate quality evidence, the panel concluded that the benefits far outweigh the risks for patients with established RA treated with a targeted approach compared to a non-targeted approach (Figure 4).

PICO B.2. The recommendation is **strong** despite the low quality of evidence because DMARD monotherapy is available as a less costly first-line therapy that has an extensive safety record with well-documented clinical efficacy, a large body of clinical experience, and familiarity among rheumatologists. The panel also voted that MTX should be the preferred initial DMARD for most patients with established RA who have never taken a DMARD.

PICO B.3. The recommendation is *conditional* despite the published positive tofacitinib efficacy data because the balance of benefit (tofacitinib slightly more efficacious), risk (long-term safety of tofacitinib is currently not well-known versus the well-known long-term safety of MTX), and cost considerations (MTX is less expensive than tofacitinib), favored MTX overall.

PICO B.4. The recommendation is *conditional* because the evidence is of low quality. The evidence supporting an incremental benefit for double DMARD therapy over DMARD monotherapy is indirect, and the evidence for differences in side effects is imprecise.

PICO B.5. The recommendation is **strong** despite moderate to very low quality of evidence because for a patient failing DMARD monotherapy, clinical experience and indirect evidence support the benefits of adding these treatment options, and recommending no treatment is not an option. The panel also voted that biologic therapy should be used in combination with MTX, when possible, due to superior efficacy of this combination over biologic monotherapy.

PICO B.6. The recommendation is **strong** because, compared to TNFi monotherapy, TNFi therapy has superior efficacy when used in combination with MTX, based on high quality evidence.

PICOs B.12 and B.14. The recommendation is *conditional* because 1) there is evidence for rituximab's efficacy in patients who have already received TNFi therapy, and for tocilizumab's superiority over a TNFi in patients already receiving MTX/DMARDs, and 2) there is evidence for efficacy of tocilizumab monotherapy.

PICOs B.13 and B.15. The recommendation is *conditional* because 1) the evidence is of very low quality, and 2) there is not enough difference in efficacy between non-TNF biologics and tofacitinib to outweigh the long-term safety data and the amount of experience associated with non-TNF biologics.

PICOs B.16 and B.17. The recommendation is *conditional* because 1) the evidence is of very low quality, 2) non-TNF biologics have longer-term safety data compared to tofacitinib, 3) there is greater long-term clinical experience with non-TNF biologics compared to tofacitinib, 4) there is not enough difference in efficacy between non-TNF biologics and tofacitinib to outweigh the longer-term safety data and greater amount of experience with non-TNF biologics, and 5) the fact that other non-TNF biologics with different mechanisms of action may be efficacious and worth trying.

PICOs B.8, B.9, B.10, and B.11. The recommendation is *conditional* because 1) the evidence is of very low quality, and 2) there is limited evidence, especially for the long-term safety data for tofacitinib.

PICOs B.23 and B.24. The recommendation is *conditional* because 1) the evidence is of very low quality, 2) improvement in outcomes as measured by the Health Assessment Questionnaire is numerically higher for patients randomized to tofacitinib compared to TNFi in an RCT; however, long-term safety data for tofacitinib are not yet available, and 3) some patients may prefer an oral formulation over an injection.

PICOs B.21 and B.22. The recommendation is *conditional* for the same reasons as cited above for PICOs B.16 and B.17 (except reason #2).

PICOs B.19 and B.20. The recommendation is *conditional* for the same reasons as cited above for PICOs B.23 and B.24.

Recommendations for patients with Established RA[1]	Level of Evidence (evidence reviewed)
1. Regardless of disease activity level, use a treat-to-target strategy rather than a non-targeted approach (PICO B.1).	**Moderate (44-46)**
2. If the disease activity is low, in patients who have never taken a DMARD, use DMARD monotherapy (MTX preferred) over a TNFi (PICO B.2).	**Low (47,48)**
3. *If the disease activity is moderate or high in patients who have never taken a DMARD:* • *use DMARD monotherapy (MTX preferred) over tofacitinib (PICO B.3).* • *use DMARD monotherapy (MTX preferred) over combination DMARD therapy (PICO B.4).*	*High (49)* *Moderate (18,20-25)*
4. **If disease activity remains moderate or high despite DMARD monotherapy, use combination traditional DMARDs *or* add a TNFi *or* a non-TNF biologic *or* tofacitinib (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (PICO B.5).**	**Moderate to Very low (23,26,29,30,47,48,50-59)**
5. If disease activity remains moderate or high despite TNFi therapy in patients who are currently not on DMARDs, add one or two DMARDs to TNFi therapy rather than continuing TNFi therapy alone (PICO B.6).	**High (60-65)**
6. *If disease activity remains moderate or high despite use of a single TNFi:* • *use a non-TNF biologic, with or without MTX, over another TNFi with or without MTX (PICO B.12 and B.14).* • *use a non-TNF biologic, with or without MTX, over tofacitinib with or without MTX (PICO B.13 and B.15).*	*Low to Very low (66-72)* *Very low*[4]
7. *If disease activity remains moderate or high despite use of a single non-TNF biologic, use another non-TNF biologic, with or without MTX, over tofacitinib, with or without MTX (PICO B.16 and B.17).*	*Very low*[4]
8. *If disease activity remains moderate or high despite use of multiple (2+) sequential TNFi therapies, first use a non-TNF biologic, with or without MTX, over another TNFi or tofacitinib (with or without MTX) (PICO B.8, B.9, B.10, B.11).*	*Very low (73-75)*
9. *If the disease activity still remains moderate or high despite the use of multiple TNFi therapies, use tofacitinib, with or without MTX, over another TNFi, with or without MTX, if use of a non-TNF biologic is not an option (PICO B.23 and B.24).*	*Low (29,30)*
10. *If disease activity remains moderate or high despite use of at least one TNFi and at least one non-TNF-biologic:* • *first use another non-TNF biologic, with or without MTX, over tofacitinib (PICO B.21 and B.22).* • *If disease activity remains moderate or high, use tofacitinib, with or without MTX, over another TNFi (PICO B.19 and B.20).*	*Very low (29,30)* *Very low (29)*
11. *If disease activity remains moderate or high despite use of DMARD, TNFi, or non-TNF biologic therapy, add short-term, low dose glucocorticoid therapy (PICO B.26 and B.27).*	*High to Moderate (33,41,76,77)*
12. *If disease flares in patients on DMARD, TNFi, or non-TNF biologic therapy, add short-term glucocorticoids at the lowest possible dose and the shortest possible duration (PICO B.28 and B.29).*	*Very low (40-43)*
13. *If the patient is in remission:* • *taper DMARD therapy (PICO B.31)*[2]**.** • *taper TNFi, non-TNF biologic, or tofacitinib (PICO B.33, B.35, B.37) (please also see #15).*	*Low*[3] *(78)* *Moderate to Very low*[3] *(79,80)*
14. **If disease activity is low:** • **continue DMARD therapy (PICO B.30).** • **continue TNFi, non-TNF biologic or tofacitinib rather than discontinuing respective medication (PICO B.32, B.34 and B.36).**	**Moderate (78)** **High to Very low (79,80)**
15. **If the patient's disease is in remission, do not discontinue all RA therapies (PICO B.38).**	**Very low**[4]

Figure 4. Summary of 2015 American College of Rheumatology (ACR) recommendations for the treatment of Established rheumatoid arthritis (RA). Green and bolded = strong recommendation. A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. Yellow and italicized = conditional recommendation: The desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. A treatment recommendation favoring one medication over another means that the preferred medication would be the recommended first option and the nonpreferred medication may be the second option. Favoring one medication over the other does not imply that the nonfavored medication is contraindicated for use; it is still an option. Therapies are listed alphabetically; azathioprine, gold, and cyclosporine were considered but not included. Disease-modifying antirheumatic drugs (DMARDs) include hydroxychloroquine, leflunomide, methotrexate (MTX), and sulfasalazine. 1 = definition of established RA is based on the 1987 ACR RA classification criteria (81), since the 2010 ACR/European League Against Rheumatism RA classification allows classification of a much earlier disease state (82). 2 = tapering means scaling back therapy (reducing dose or dosing frequency), not discontinuing it. Tapering should be considered an option and not be mandated. If done, tapering must be conducted slowly and carefully, watching for increased disease activity and flares. Even for patients whose RA is in remission, there is some risk of flare when tapering. 3 = evidence is rated low quality or moderate to very low quality because some evidence reviewed for this recommendation was indirect and included studies with discontinuation rather than tapering of therapy or since studies involved patients achieving low disease activity rather than remission. 4 = no studies were available, leading to very low quality evidence, and the recommendation was based on clinical experience. PICO = population, intervention, comparator, and outcomes; TNFi = tumor necrosis factor inhibitor. For definitions and descriptions, see Table 1.

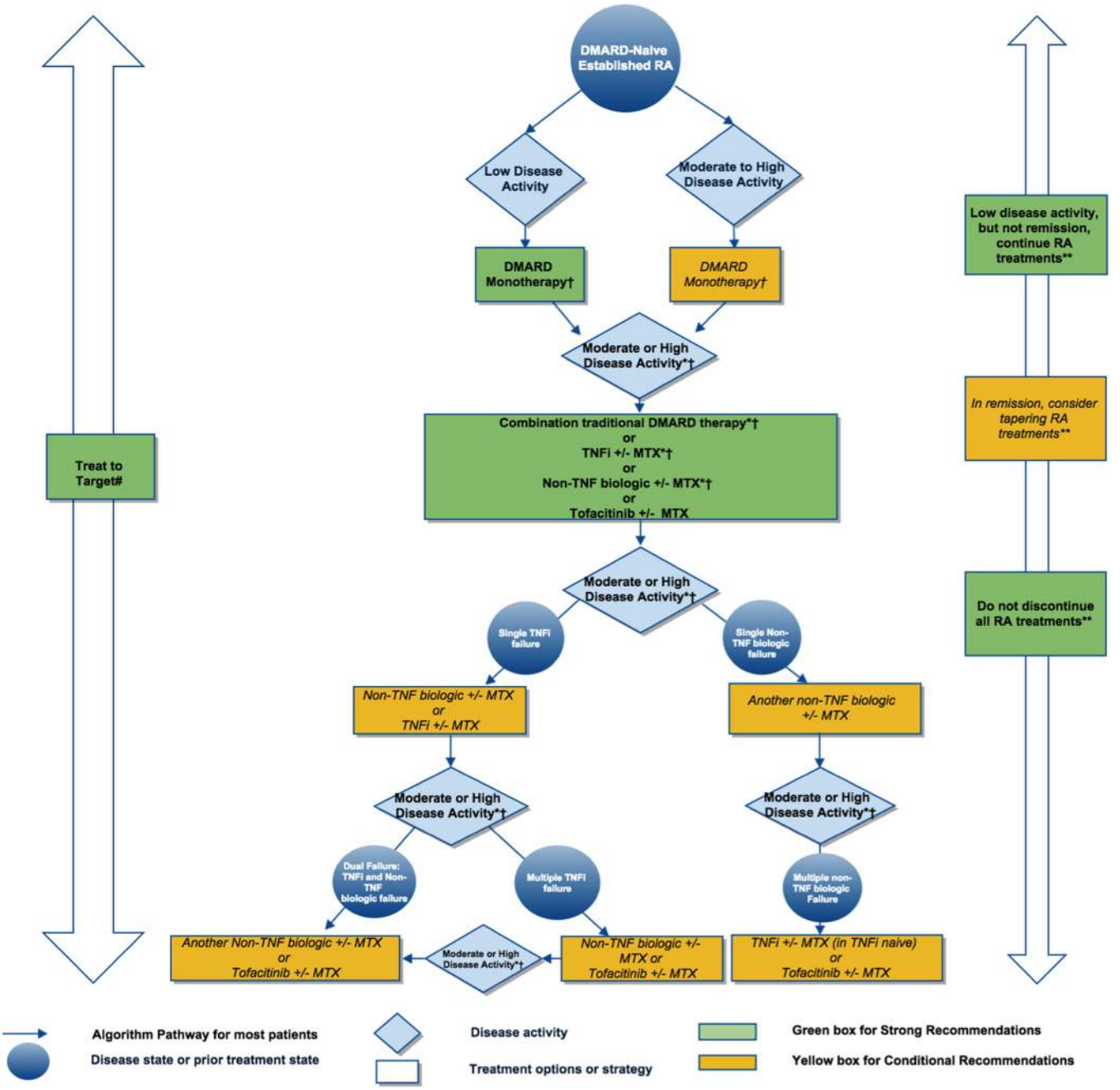
DMARD-Naive Established RA
Low Disease Activity
Moderate to High Disease Activity
DMARD Monotherapy†
DMARD Monotherapy†
Moderate or High Disease Activity*†
Combination traditional DMARD therapy*† or TNFi +/- MTX*† or Non-TNF biologic +/- MTX*† or Tofacitinib +/- MTX
Moderate or High Disease Activity*†
Single TNFi failure
Single Non-TNF biologic failure
Non-TNF biologic +/- MTX or TNFi +/- MTX
Another non-TNF biologic +/- MTX
Moderate or High Disease Activity*†
Moderate or High Disease Activity*†
Dual Failure: TNFi and Non-TNF biologic failure
Multiple TNFi failure
Multiple non-TNF biologic Failure
Another Non-TNF biologic +/- MTX or Tofacitinib +/- MTX
Moderate or High Disease Activity*†
Non-TNF biologic +/- MTX or Tofacitinib +/- MTX
TNFi +/- MTX (in TNFi naive) or Tofacitinib +/- MTX
Treat to Target#
Low disease activity, but not remission, continue RA treatments**
In remission, consider tapering RA treatments**
Do not discontinue all RA treatments**
Algorithm Pathway for most patients
Disease state or prior treatment state
Disease activity
Treatment options or strategy
Green box for Strong Recommendations
Yellow box for Conditional Recommendations

Figure 5. 2015 American College of Rheumatology (ACR) recommendations for the treatment of Established rheumatoid arthritis (RA), defined as disease duration ≥6 months, or meeting the 1987 ACR classification criteria (81). Due to complexity of management of established RA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show the key recommendations. For a complete list of recommendations, please refer to the Results. * = consider adding low-dose glucocorticoids (≤10 mg/day of prednisone or equivalent) in patients with moderate or high RA disease activity when starting traditional disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure. † = also consider using short-term glucocorticoids (defined as <3 months treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible duration to provide the best benefit-risk ratio for the patient. # = treatment target should ideally be low disease activity or remission. ** = tapering denotes scaling back therapy (reducing dose or dosing frequency), not discontinuing it and if done, must be conducted slowly and carefully. For the level of evidence supporting each recommendation, see the related section in the Results. This figure is derived from recommendations based on PICO (population, intervention, comparator, and outcomes) questions B.1 to B.38. For definitions of disease activity (categorized as low, moderate, or high) and descriptions, see Tables 1 and 2. MTX = methotrexate; TNFi = tumor-necrosis factor inhibitor.

Table 3. Recommendations for optimal followup laboratory monitoring intervals for complete blood count, liver transaminase levels, and serum creatinine levels for patients with rheumatoid arthritis receiving disease-modifying antirheumatic drugs*

	Monitoring interval based on duration of therapy‡		
Therapeutic agents†	**<3 months**	**3–6 months**	**>6 months**
Hydroxychloroquine	None after baseline§	None	None
Leflunomide	2–4 weeks	8–12 weeks	12 weeks
Methotrexate	2–4 weeks	8–12 weeks	12 weeks
Sulfasalazine	2–4 weeks	8–12 weeks	12 weeks

* More frequent monitoring is recommended within the first 3 months of therapy or after increasing the dose, and the outer bound of the monitoring interval is recommended beyond 6 months of therapy. Adapted from ref. 6.
† Listed alphabetically.
‡ The panel indicated that patients with comorbidities, abnormal laboratory results, and/or multiple therapies may require more frequent laboratory testing than what is generally recommended laboratory monitoring for disease-modifying antirheumatic drugs in the table.
§ See ref. 6 for baseline monitoring recommendations.

PICOs B.26 and B.27. The recommendation is *conditional* because the risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and duration of therapy is short.

PICOs B.28 and B.29. The recommendation is *conditional* because 1) the evidence is of very low quality, and 2) the risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and duration of therapy is short.

The panel also made several recommendations related to tapering therapy, with the following general caveats: 1) "Tapering" is defined as scaling back therapy 1 medication at a time (reducing dose or dosing frequency), 2) Patients' values and preferences should drive decisions related to tapering, 3) A comprehensive plan to monitor disease activity and address possible flares is implemented, and 4) Prior to tapering, RA patients, including those in sustained remission, are informed of the risk of flare.

PICOs B.31, B.33, B.35, and B.37. The recommendation is *conditional* because 1) the evidence is of low quality, 2) while tapering carries a risk of flare, minimizing therapy may decrease toxicity, and/or cost, and lowers the risk of treating patients unnecessarily.

PICOs B.30, B.32, B.34, and B.36. The recommendation is **strong** because based on clinical observations and experience only a small minority of patients with low disease activity (not remission) is able to successfully discontinue all RA therapy.

PICO B.38. The recommendation is **strong** despite very low quality of evidence because based on clinical experience, the risk of RA flare and the need for resumption of therapy are high, if all RA therapies are discontinued.

The Voting Panel also voted on 2 additional PICO questions (B.7 and B.18) to fill the remaining gaps in the treatment algorithm after the initial voting (Figure 5). Both compare therapy with no therapy. We followed the GRADE methodology and the same process for these PICO questions.

PICO B.7. If disease activity remains moderate or high despite the use of a single TNFi, the recommendation is *conditional* for using another TNFi rather than not using a TNFi. The recommendation is *conditional* because both evidence from TNFi studies and clinical experience support response to a second TNFi in a significant proportion of patients, especially in the presence of secondary failure (i.e., a TNFi worked initially and then stopped working). For additional recommendations related to this patient population, see PICOs B.12, B.15, B.23, and B.24.

PICO B.18. If disease activity remains moderate or high despite the use of multiple non-TNF biologics and the patient is TNFi-naive, the recommendation is *conditional* for using TNFi rather than not using TNFi. The recommendation is *conditional* because the evidence is of very low quality. Although there are no trials of patients with multiple non-TNF biologic failures, if non-TNF biologics have not been effective and TNFi therapy has not yet been given, then TNFi therapy should be tried, unless there are contraindications for its use.

Recommendations for laboratory monitoring for DMARDs and TB screening in patients receiving biologics or tofacitinib

The panel endorsed the recommendations previously published in the 2008 recommendations and in the 2012 update to be included in the 2015 recommendations (Table 3 and Figure 6). The panel indicated that in the absence of significant new knowledge, development of an alternate rec-

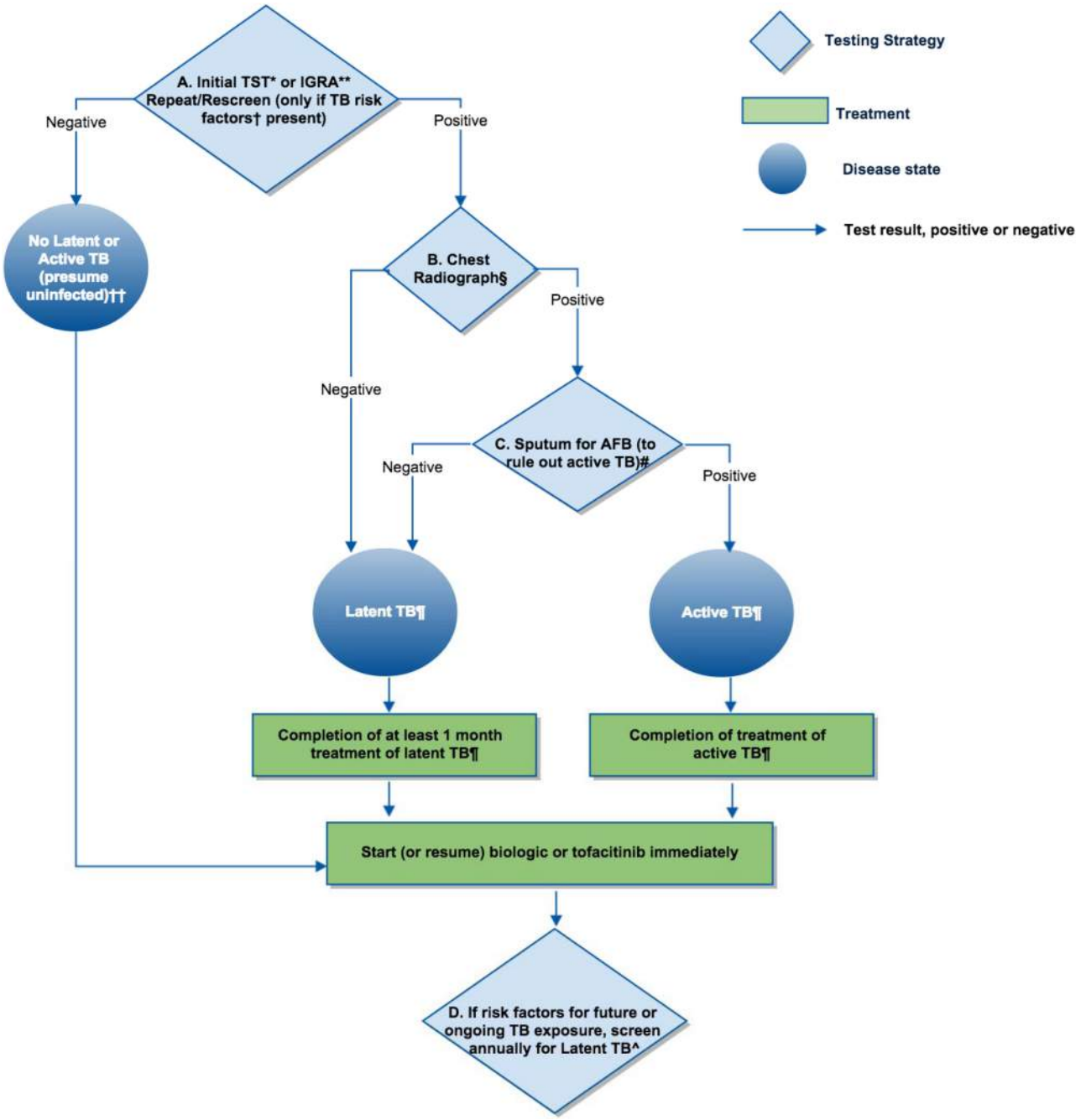
Testing Strategy
Treatment
Disease state
Test result, positive or negative
A. Initial TST* or IGRA** Repeat/Rescreen (only if TB risk factors† present)
Negative
Positive
No Latent or Active TB (presume uninfected)††
B. Chest Radiograph§
Positive
Negative
C. Sputum for AFB (to rule out active TB)#
Negative
Positive
Latent TB¶
Active TB¶
Completion of at least 1 month treatment of latent TB¶
Completion of treatment of active TB¶
Start (or resume) biologic or tofacitinib immediately
D. If risk factors for future or ongoing TB exposure, screen annually for Latent TB^

Figure 6. Tuberculosis (TB) screening algorithm for biologics or tofacitinib (endorsed and modified from the 2012 American College of Rheumatology RA treatment recommendations). The Voting Panel reviewed and endorsed the 2012 TB screening algorithm with 1 change, that tofacitinib should be included alongside biologics. * = anergy panel testing is not recommended. ** = interferon-gamma release assay (IGRA) is preferred if patient has a history of BCG vaccination. † = risk factors for TB exposure are defined based on a publication from the US Centers for Disease Control and Prevention as: close contacts of persons known or suspected to have active TB, foreign-born persons from areas that have a high incidence of active TB (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia), persons who visit areas with a high prevalence of active TB, especially if visits are frequent or prolonged, residents and employees of congregate settings whose clients are at increased risk for active TB (e.g., correctional facilities, long-term care facilities, and homeless shelters), health care workers who serve clients who are at increased risk for active TB, populations defined locally as having an increased incidence of latent *Mycobacterium tuberculosis* infection or active TB, possibly including medically underserved, low-income populations, or persons who abuse drugs or alcohol, and infants, children, and adolescents exposed to adults who are at increased risk for latent *M tuberculosis* infection or active tuberculosis (159,160). †† = if patient is immunosuppressed and false-negative results more likely, consider repeating screening test(s) with tuberculin skin test (TST) or IGRA. § = chest radiography may also be considered when clinically indicated in patients with risk factors, even with a negative result on repeat TST or IGRA. # = obtain respiratory (e.g., sputum, bronchoalveolar lavage) or other samples as clinically appropriate for acid-fast bacilli (AFB) smear and culture. Consider referral to TB specialist for further evaluation and treatment. ¶ = in a patient diagnosed as having latent or active TB, consider referral to a specialist for the recommended treatment. ^ = patients who test positive for TST or IGRA at baseline (pretreatment) often remain positive for these tests even after successful treatment of TB. These patients need monitoring for clinical signs and symptoms of recurrent TB disease, since repeating tests will not allow help in diagnosis of recurrent TB. The level of evidence supporting each recommendation for TB reactivation was derived from consensus opinion of experts, case studies, or standards of care. The level of evidence for initiation of biologics in patients being treated for latent TB infection was higher, with data derived from a single randomized trial or nonrandomized studies. Adapted from ref. 5.

ommendation was not warranted with one exception: the Voting Panel recommended that the same TB screening algorithm as described for biologics should be followed for patients receiving tofacitinib. For additional details (including baseline laboratory monitoring), please see the 2008 and 2012 guidelines (5,6).

Recommendations in RA patients with high-risk comorbidities

Recommendations are provided in Figure 7. An executive summary of these recommendations is available in Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/acr.22783/abstract.

Congestive heart failure

PICOs C.1, C.2, C.3, C.4, C.5, and C.6. The recommendations are *conditional* because the evidence is of very low quality. The Voting Panel noted that there are no reports of exacerbation of heart failure using non-TNF biologics and the US Food and Drug Administration (FDA) warns against using TNFi in this population based on worsening of congestive heart failure with TNFi in the Adverse Event Reporting System database. A TNFi should only be used if there are no other reasonable options, and then, perhaps, only in compensated heart failure (83,84) (Figure 7).

Hepatitis B

To address hepatitis B, the AASLD practice guidelines were reviewed (85,86). These guidelines suggest that immunosuppressive therapy can be safely utilized when prophylactic antiviral therapy is prescribed concomitantly.

PICO D.1. The recommendation is **strong** despite very low evidence (85–92) because clinical experience supports the benefits of treating these RA patients with active disease, and an absence of additional harms, if patients are receiving concomitant effective antiviral treatment. The Voting Panel further specified that for a patient with natural immunity from prior exposure to hepatitis B (i.e., hepatitis B core antibody positive, normal liver function tests, and hepatitis B surface [HBs] antibody positive and HBs antigen negative), RA treatment should be the same as that of unexposed patients, as long as the patient's viral load is monitored regularly (117,118), conservatively, every 6–12 months. For patients with chronic hepatitis B who are untreated, referral for antiviral therapy is appropriate prior to immunosuppressive therapy (88,119–124). A recent review summarized this evidence (125).

Hepatitis C

PICO E.1. The recommendation is *conditional* because the evidence is of very low quality, i.e., indirect evidence from patient populations other than RA (92–103). The evidence suggests that these RA patients with hepatitis C virus (HCV) infection should *not* be treated differently than RA patients who do not have hepatitis C. The Voting Panel recommended that rheumatologists collaborate with gastroenterologists and/or hepatologists to monitor patients receiving antiviral therapy. This is important considering the recent availability of highly effective therapy for HCV, which might lead to a greater number of HCV patients being treated successfully.

PICO E.2. The recommendation is *conditional* because the evidence is of very low quality. For patients with HCV infection or exposure, the safety of biologic therapy was addressed indirectly by 2 RCTs and a variety of small observational studies including case series (92–103). Much of this research was not confined to individuals with RA. This very low-level evidence suggests that TNFi therapy can be safely administered in HCV-positive patients, if treatment with antiviral therapy is used. One small, long-term observational study of HCV-positive individuals receiving TNFi immunosuppression found that increased HCV activity was associated with the absence of concomitant antiviral therapy (93). In a small RCT of HCV-positive individuals with RA who did not require antiviral therapy, neither patients treated with MTX nor patients treated with TNFi therapy demonstrated significant change in viral load (98). The Voting Panel recommended that rheumatologists collaborate with gastroenterologists and/or hepatologists in recommending individualized treatment based on other comorbidities, reason(s) for not receiving HCV treatment, and the need to minimize immunosuppression, and consider using DMARDs other than MTX or leflunomide, such as sulfasalazine *or* hydroxychloroquine.

Malignancy

Previous melanoma and non-melanoma skin cancer. Separate PICO questions addressed melanoma and non-melanoma skin cancer, but the recommendations were similar, and therefore were combined.

PICOs F.1, F.2, F.3, and F.4. The recommendation is *conditional* because 1) the evidence is of very low quality, 2) due to potentially lower risk of recurrence of skin cancer with DMARDs versus other therapies based on clinical experience and 2 retrospective studies (104,105), and 3) a lack of data and knowledge about some of the mechanisms of action of biologics and tofacitinib, which may potentially contribute to an increased cancer risk. DMARDs were considered less immunosuppressive than biologics. The Voting Panel also stated that host factors may vary and may influence the risk of

High-risk condition	Recommendation	Level of Evidence (evidence reviewed)
Congestive heart failure[1]		
CHF	*Use combination DMARDs or non-TNF biologic or tofacitinib over TNFi (PICO C.1, C.2 and C.3).*	*Moderate to Very low (83,84)*
CHF worsening on current TNFi therapy	*Use combination DMARDs or non-TNF biologic or tofacitinib over another TNFi (PICO C.4, C.5 and C.6).*	*Very low[7]*
Hepatitis B[2]		
Active Hepatitis B infection and receiving/received effective antiviral treatment	**Same recommendations as in patients without this condition (PICO D.1).**	**Very low (85-92)**
Hepatitis C[2]		
Hepatitis C infection and receiving/received effective antiviral treatment	*Same recommendations as in patients without this condition (PICO E.1).*	*Very low (92-103)*
Hepatitis C infection and not receiving or requiring effective antiviral treatment	*Use DMARDs over TNFi (PICO E.2)[3].*	*Very low (92-103)*
Past history of treated or untreated malignancy[4]		
Previously treated or untreated skin cancer (non-melanoma or melanoma)	*Use DMARDs over biologics in melanoma (PICO F.1).* *Use DMARDs over tofacitinib in melanoma (PICO F.2).* *Use DMARDs over biologics in non-melanoma (PICO F.3).* *Use DMARDs over tofacitinib in non-melanoma (PICO F.4).*	*Very low (104-106)*
Previously treated lymphoproliferative disorder	**Use rituximab over TNFi (PICO G.1).**	**Very low (105,107)**
Previously treated lymphoproliferative disorder	*Use combination DMARD or abatacept or tocilizumab over TNFi* (PICO G.2, G.3 and G.4).	*Very low (105,107)*
Previously treated solid organ malignancy	*Same recommendations as in patients without this condition (PICO H.1).*	*Very low (105,108)*
Previous Serious Infection(s)[5]		
Previous Serious infection(s)	*Use combination DMARD over TNFi (PICO I.1)[5].* *Use abatacept over TNFi (PICO I.2)[6].*	*Very low (109-116)*

Figure 7. Summary of 2015 American College of Rheumatology recommendations for high-risk patients with established rheumatoid arthritis with moderate or high disease activity and congestive heart failure (CHF), hepatitis B or C, past history of malignancy, or serious infection(s). Green and bolded = strong recommendation. A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. Yellow and italicized = conditional recommendation. The desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. A treatment recommendation favoring one medication over another means that the preferred medication would be the recommended first option and the nonpreferred medication may be the second option. Favoring one medication over the other does not imply that the nonfavored medication is contraindicated for use; it is still an option. 1 = conditional recommendations supported by evidence level ranging from moderate level to no evidence, supported by clinical experience and the Food and Drug Administration safety warning with tumor necrosis factor inhibitors (TNFi). 2 = strong recommendations for Hepatitis B were largely based upon the recent American Association for the Study of Liver Diseases practice guidelines (85,86) and clinical experience; conditional recommendations for Hepatitis C were largely supported by very low level evidence based upon case series and clinical experience. 3 = consider using DMARDs other than methotrexate or leflunomide, such as sulfasalazine *or* hydroxychloroquine. 4 = conditional recommendations supported by level of evidence ranging from very low to no evidence, are largely based upon expert opinion and clinical experience. 5 = conditional recommendation was supported by very low level evidence. 6 = there was no consensus for making recommendations regarding the use of rituximab over TNFi or the use of tocilizumab over TNFi in this setting, due to indirect evidence (e.g., no comparison to TNFi or including patients with tuberculosis) and differences of opinion. In 1 study, compared to patients who restarted their previous TNFi following hospitalized infections, patients who switched to abatacept exhibited lower risk of subsequent hospitalized infections among the therapies examined. 7 = no studies were available, leading to very low quality evidence, and the recommendation was based on clinical experience. DMARDs = disease-modifying antirheumatic drugs; PICO = population, intervention, comparator, and outcomes.

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal[1]	Influenza (intramuscular)	Hepatitis B[2]	Human Papilloma	Herpes Zoster[3]
Before initiating therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓	✓	✓ *(PICO J.1)*[5]
Non-TNF biologics	✓	✓	✓	✓	✓ *(PICO J.1)*[5]
While already taking therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]
Non-TNF biologics[4]	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]

Figure 8. 2015 American College of Rheumatology (ACR) recommendations update regarding the use of vaccines in patients with rheumatoid arthritis (RA) starting or currently receiving disease-modifying antirheumatic drugs (DMARDs) or biologics. ✓ = recommend vaccination when indicated (based on age and risk). Red indicates vaccinations not recommended. The panel endorsed all 2012 RA treatment recommendations for vaccination with 1 exception (see footnote 6), and re-voted only for certain immunization recommendations in patients receiving biologics. All recommendations were *conditional*, except that the panel strongly recommended (in green) using appropriately indicated killed/inactivated vaccines in patients with early or established RA who are currently receiving biologics. Evidence level was very low for recommendations based on population, intervention, comparator, and outcomes (PICOs) J.1, J.2, J.3, J.4, and J.5. Evidence level for the remaining recommendations that were endorsed from the 2012 ACR RA treatment guideline was similar (on a different scale). 1 = the Centers for Disease Control and Prevention (CDC) also recommends a one-time pneumococcal revaccination after 5 years for persons with chronic conditions such as RA. The CDC recommends pneumococcal conjugate vaccine (PCV13 or Prevnar 13) for all children younger than 5 years of age, all adults ≥65 years, and persons 6−64 years of age with certain medical conditions. Pneumovax is a 23-valent pneumococcal polysaccharide vaccine (PPSV23) that is currently recommended for use in all adults ≥65 years old and for persons who are ≥2 years old and at high risk for pneumococcal disease (e.g., those with sickle cell disease, HIV infection, or other immunocompromising conditions). PPSV23 is also recommended for use in adults 19−64 years of age who smoke cigarettes or who have asthma (http://www.cdc.gov/vaccines/vpd-vac/pneumo/default.htm?s_cid=cs_797). 2 = if hepatitis B risk factors are present (e.g., intravenous drug abuse, multiple sex partners in the previous 6 months, health care personnel). 3 = the panel conditionally recommended that in RA patients ages ≥50 years, the herpes zoster vaccine should be given before the patient receives biologic therapy or tofacitinib for their RA. 4 = response to certain killed vaccines may be reduced after rituximab therapy. 5 = the panel conditionally recommended giving the herpes zoster vaccine before the patient receives biologic therapy or tofacitinib for their RA in both early or established RA patients ages ≥50 years (PICO J.1). The panel also voted that after giving the herpes zoster vaccine, there should be a 2-week waiting period before starting biologics. 6 = the panel strongly recommended that in patients with early or established RA who are currently receiving biologics, appropriately indicated killed/inactivated vaccines should be used (PICOs J.4 and J.5). 7 = the panel conditionally recommended that in early or established RA patients who are currently receiving biologics, live attenuated vaccines such as the herpes zoster (shingles) vaccine should not be used (PICOs J.2 and J.3). TNFi = tumor necrosis factor inhibitor. For definitions and descriptions, see Table 1. Adapted from ref. 5.

recurrence of skin cancer. Even though biologics were not the first option, several Voting Panel members indicated that if the joint disease was moderately or highly active in the setting of a low-grade melanoma or non-melanoma skin cancer that had been previously treated, biologics would be an acceptable option with close skin surveillance in conjunction with a dermatologist.

It is important to note that although the panel voting on PICO F.3 (using a DMARD rather than a biologic for patients with a prior history of non-melanoma skin cancer) achieved the necessary 70% threshold for consensus, there was 1 Voting Panel member with a dissenting view that the risk difference between DMARDs and biologics in RA patients with a previously treated or untreated non-melanoma skin cancer may be insignificant, and 2 other Voting Panel members also shared some of these concerns but voted conditionally in favor of DMARDs.

Previous lymphoproliferative disorders

PICO G.1. The recommendation is **strong** despite very low quality evidence because rituximab is an approved treatment for some of these disorders and the best available clinical trial data suggest that there is a signal in clinical trials of induction and/or an increased risk of lymphoma in patients treated with TNFi (105,107).

PICOs G.2, G.3, and G.4. The recommendation is *conditional* because 1) the evidence is of very low quality (105,107), 2) there is a lack of evidence for combination DMARD therapy versus TNFi (PICO G.2), and 3) as described in PICO G.1, there is a possible increased risk of lymphoma associated with TNFi, but there is no evidence that abatacept or tocilizumab increases this risk (PICOs G.3 and G.4).

Previous solid organ cancer

PICO H.1. The recommendation is *conditional* because the evidence is of very low quality (105,108).

Serious infections

PICOs I.1 and I.2. The recommendation is *conditional* because 1) the evidence is of very low quality (indirect), as most trials excluded patient groups with a high risk of serious infections, and 2) rheumatologists have greater experience with DMARDs compared to TNFi in patients with previous serious infections. The recommendation regarding abatacept is conditional because the evidence is very low quality. In one study, compared to patients who restarted their previous TNFi following hospitalized infections, patients who switched to abatacept exhibited the lowest risk of subsequent hospitalized infection among the therapies examined (109).

Recommendations for use of vaccines in RA patients receiving DMARD and/or biologic therapy

Recommendations for use of vaccines in RA patients on DMARD and/or biologic therapy are provided in Figure 8.

PICO J.1. The recommendation is *conditional* because the evidence is of very low quality. The CDC has recommended the herpes zoster vaccine for people ages ≥60 years in the general population, but not for adults ages 50–59 years, even though the FDA approved the vaccine in adults ≥50 years. The CDC reconsidered the use of vaccination in people 50–59 years in 2013 and decided not to change its current recommendation for the general population, but did not vote (126). Our Voting Panel considered these recommendations and, because the immune systems of RA patients are compromised by the disease or by medications, the panel agreed that patients with RA ages ≥50 years should be vaccinated before receiving biologic or tofacitinib therapy because the benefits of doing so likely outweigh the risks in this population.

PICOs J.2 and J.3. The recommendation is *conditional* because 1) the evidence is of very low quality (127,128), and 2) there is a safety warning about the use of live vaccines in patients receiving biologics (127,128) (see Zostavax packet insert available at https://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi2.pdf).

PICOs J.4 and J.5. The recommendation is **strong** despite very low quality of evidence (129–135) because of the documented benefit of killed vaccines in adults and no significant concerns of harm in RA patients receiving biologics, as per the general guidance from the CDC. Clinicians should consult the CDC recommendations for killed vaccines (136–140). Responses to some killed vaccines may be reduced after rituximab therapy (141) and possibly after MTX therapy. Whenever possible, vaccines should be given *prior to* receiving therapy.

In addition to these recommendations, the Voting Panel endorsed the vaccination recommendations made in 2012, with the 1 exception mentioned above, i.e., responses to certain killed vaccines may be reduced after rituximab therapy (141) (Figure 8).

DISCUSSION

The 2015 ACR RA treatment guideline addresses the use of DMARDs, biologics, tofacitinib, and glucocorticoids in early and established RA and the use of various treatment approaches in frequently encountered clinical scenarios, including treat-to-target, switching between therapies, tapering of therapy, the use of biologics and DMARDs in high-risk RA patients, vaccination in patients with RA receiving DMARDs or biologics, TB screening with biologics or tofacitinib, and laboratory monitoring with DMARDs. The recommendations aim to provide guidance for clinicians and patients in an era of rapid advances in the treatment of RA. These recommendations were developed using scientific evidence, a rigorous, well-defined guideline development methodology, and a group consensus process. Compared to earlier treatment guidelines, there were several differences in the development of the 2015 RA treatment recommendations.

First, we used the GRADE methodology because it provides an internationally accepted systematic approach to guideline development. PICO questions were developed with the intended patient populations and outcomes explicitly listed. Before beginning the evidence synthesis, we posted the PICO questions online and solicited feedback and comments from the ACR membership. We also noted dissenting views. An example is the dissenting view related to the conditional recommendation for DMARDs over biologics for RA patients with previously treated or untreated non-melanoma skin cancer. Even though the panel reached consensus with 90% voting in favor, 1 panel member had a dissenting opinion and voted for biologic therapy over DMARD therapy in this situation. It should be noted that melanoma and non-melanoma were considered and voted on separately by the panel but that the final recommendations were similar for both situations and, therefore, are presented as a single recommendation.

Unlike previous ACR RA guidelines, the panel decided to base these new recommendations only on patients' disease activity level rather than including both disease activity and prognosis. The justification for this approach was that adding another variable (prognosis) to the PICO questions would have made the project much less feasible. Also, the Content Panel and the Voting Panel agreed that disease prognosis was largely captured in the concept of disease activity and that information regarding prognosis was unlikely to further contribute to decision-making.

Recommendations related to immunization and treatment in patients with RA and coexistent viral hepatitis B or C were informed primarily by the CDC (138) and the AASLD guidelines (85,86), respectively, and require fur-

ther explanation. The panel made a *conditional* recommendation to use herpes zoster immunization at age 50 and older prior to starting biologics, considering the higher infection risk due to RA and its treatments. This is consonant with the FDA approval for the use of herpes zoster vaccine in adults ages ≥50 years, and despite current CDC recommendations to use the vaccine in the general population (i.e., not RA patients) at ages ≥60 years. The panel also stated that as long as RA patients with viral hepatitis were started on the appropriate antiviral treatments for hepatitis B and C prior to initiation of RA therapy, they could be treated similarly to RA patients without these chronic viral infections. Case reports, case series, and small observational studies of RA patients with hepatitis B or C who have been treated with medications for RA provided additional supportive evidence. However, the data are limited in these clinical settings, and close monitoring of such patients and consultation with the appropriate specialists is advised.

The Voting Panel strongly recommended the use of combination traditional DMARDs *or* addition of a TNFi *or* a non-TNF biologic *or* tofacitinib for patients with established RA with moderate or high disease activity despite DMARD monotherapy. After carefully considering the evidence, the panel concluded that the limited direct comparative evidence for these therapies in this clinical situation precluded recommending a ranking of these treatment options.

Due to rapidly evolving knowledge for the treatment of RA, some recommendations may be outdated by the time they are published due to the emergence of new evidence. Examples include new data on tapering and discontinuation of therapies in early RA (142) and treat-to-target (143). The short half-life of treatment recommendations is also related to the rigorous and time-consuming process of guideline development used by the ACR, which complies with guidance from the National Academy of Medicine (formerly the Institute of Medicine) and the Council for Medical Subspecialty Societies. Additional time is also required for review and endorsement of each guideline document by ACR committees, journal reviewers and editors, and the ACR Board of Directors. However, the ACR regularly updates RA guidelines and strives to shorten the time between the end of the literature review and the publication of guidelines, to make them as relevant and current as possible.

The panel provided "conditions" when making a conditional recommendation. The listed conditions were not necessarily exhaustive for each recommendation, but included those factors that were most important in determining the final panel vote. This process ensured that conditions were a direct reflection of the Voting Panel members' discussion and agreements. Although we used 70% as the agreement threshold, for 80% of the recommendations there was 90% consensus (of which 50% of the recommendations had 100% consensus). We noted that 77% of the recommendations were conditional and the remaining 23% were strong. This was partially due to the lack of evidence for common clinical situations, and our a priori decision that PICO questions should be based on what is important for a clinician and patient to know, not based on the presence or absence of the highest level of evidence. This indicates that more evidence is needed to derive strong RA recommendations in the future. A number of recommendations were strong despite low quality evidence, which is allowed according to GRADE methodology, and the Voting Panel provided justification for these recommendations.

Several important aspects of RA care were not addressed due to resource limitations, including the use of nonpharmacologic interventions (e.g., physical therapy, occupational therapy, assistive devices), use of biologics and DMARDs in other less-common conditions (e.g., new diagnosis of cancer, family history of cancer or multiple sclerosis, new diagnosis of hepatitis while receiving successful RA therapy). The Voting Panel considered the dosing issues related to glucocorticoids and MTX and believed strongly that it was not within its charge to mandate dosing. Recommendations for individual medications (e.g., various DMARDs, TNFi, non-TNF biologics) were not made, since an a priori decision was made to examine these as categories for feasibility reasons. Although we recognize that other disease activity measures have become available since the ACR endorsed 6 measures in its 2012 paper (16), it was outside the scope of this guideline effort to reevaluate measures and recommend to the ACR an updated list for possible endorsement.

A targeted literature search was performed for biosimilars, but there was too little evidence for the panel to provide recommendations on this complex issue at present. In addition, at the time of panel voting, biosimilars for RA were not yet approved for use in the US. The ACR has published a position statement on biosimilars (available at http://www.rheumatology.org/Practice-Quality/Administrative-Support/Position-Statements) that may provide some guidance for interested readers. The team recommended that biosimilars in RA therapy should be considered for future research agendas and RA guideline efforts.

The team also discussed the following topics and recommended that they be targeted for future research: use of biologics and DMARDs during the period of conception, pregnancy, and breastfeeding; treatment of RA with interstitial lung disease; laboratory monitoring for biologics/tofacitinib; and biomarker testing.

The 2015 ACR RA treatment recommendations apply to common clinical situations, since the panel considered issues common to most patients, not exceptions. In an effort to standardize terminology, the ACR has asked that the term "guideline" be used when referring to a guideline paper and the term "recommendation" when referring to an individual recommendation statement within the guideline paper. The use of the term "guideline" should not be construed as a mandate that every clinician/patient should follow the recommendations made in every clinical situation. These recommendations are not proscriptive and should be used by clinicians and patients as a guide for discussion related to RA treatments. Only a clinician's assessment, an active patient-physician dialogue, and collaborative decision-making will result in the optimal risk/benefit analysis. The best treatment decisions will be made by clinicians incorporating patients' values and preferences. Thus, the choice of the best treatment in some cases may be other options in the algorithm/recommendation rather than the first option in the treatment recommendation algorithm.

These recommendations are not intended to support payment or insurance decisions and should not be used for denial of treatments to patients. These recommendations cannot adequately convey all uncertainties and nuances of patient care in the real world. For example, a listing of all conditions entertained in each conditional recommendation is not feasible. We also noted that for newer drugs (e.g., tofacitinib), long-term experience and safety data are usually lacking, and additional data are needed to increase the confidence of clinicians in utilizing such medications.

In conclusion, the 2015 ACR RA pharmacologic treatment guideline is comprehensive and provides guidance to clinicians and patients regarding the treatment of RA. Using state-of-the-art methodology (GRADE) and a well-defined group-consensus technique, our guideline development process was systematic, explicit, and transparent. Periodic updates of this guideline, as required by the ACR for all of its guidelines, will ensure that this RA treatment guideline remains current and usable for patients and physicians for treatment decision-making in RA. Finally, the 2015 ACR RA treatment guideline is a useful tool not only to guide treatment in clinical practice but also to facilitate discussion about individualized treatment decision-making between patients and their clinicians.

ACKNOWLEDGMENTS

We thank Ms Regina Parker (ACR staff) for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, Ms Janet Joyce for help in developing the literature search strategy and performing the literature search and updates, and Ms Tamara Radar for peer reviewing the literature search strategy. We thank William Sanchez, MD (Consultant, Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN) for providing expert advice regarding treatment of RA in the presence of hepatitis B or C.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Singh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Singh, Saag, Bridges, Akl, Bannuru, Sullivan, Vaysbrot, McNaughton, Osani, Shmerling, Curtis, Furst, Parks, Kavanaugh, O'Dell, King, Leong, Matteson, Schousboe, Drevlow, Ginsberg, Grober, St.Clair, Tindall, Miller, McAlindon.

Acquisition of data. Singh, Saag, Bridges, Akl, Bannuru, Sullivan, Vaysbrot, McNaughton, Osani, Shmerling, Curtis, Furst, Parks, Kavanaugh, O'Dell, King, Leong, Matteson, Schousboe, Drevlow, Ginsberg, Grober, St.Clair, Tindall, Miller, McAlindon.

Analysis and interpretation of data. Singh, Saag, Bridges, Akl, Bannuru, Sullivan, Vaysbrot, McNaughton, Osani, Shmerling, Curtis, Furst, Parks, Kavanaugh, O'Dell, King, Leong, Matteson, Schousboe, Drevlow, Ginsberg, Grober, St.Clair, Tindall, Miller, McAlindon.

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APPENDIX A: PANEL AND TEAM MEMBERS

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Core Leadership Team: Jasvinder A. Singh, MBBS, MPH (Project Principal Investigator), Kenneth G. Saag, MD, MSc, S. Louis Bridges Jr., MD, PhD, Elie A. Akl, MD, MPH, PhD, Timothy McAlindon, MD, MPH.

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Content Panel: Robert H. Shmerling, MD, Jeffrey R. Curtis, MD, MS, MPH, Daniel E. Furst, MD, Deborah Parks, MD.

Seronegative arthropathy

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Arthritis & Rheumatology
Vol. 71, No. 10, October 2019, pp 1599–1613
DOI 10.1002/art.41042
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American College of Rheumatology
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SPECIAL ARTICLE

2019 Update of the American College of Rheumatology/ Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the health care provider in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

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Objective. To update evidence-based recommendations for the treatment of patients with ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (SpA).

Methods. We conducted updated systematic literature reviews for 20 clinical questions on pharmacologic treatment addressed in the 2015 guidelines, and for 26 new questions on pharmacologic treatment, treat-to-target strategy, and use of imaging. New questions addressed the use of secukinumab, ixekizumab, tofacitinib, tumor necrosis factor inhibitor (TNFi) biosimilars, and biologic tapering/discontinuation, among others. We used the Grading of Recommendations, Assessment, Development and Evaluation methodology to assess the quality of evidence and formulate recommendations and required at least 70% agreement among the voting panel.

Results. Recommendations for AS and nonradiographic axial SpA are similar. TNFi are recommended over secukinumab or ixekizumab as the first biologic to be used. Secukinumab or ixekizumab is recommended over the use of a second TNFi in patients with primary nonresponse to the first TNFi. TNFi, secukinumab, and ixekizumab are favored over tofacitinib. Co-administration of low-dose methotrexate with TNFi is not recommended, nor is a strict treat-to-target strategy or discontinuation or tapering of biologics in patients with stable disease. Sulfasalazine is recommended only for persistent peripheral arthritis when TNFi are contraindicated. For patients with unclear disease activity, spine or pelvis magnetic resonance imaging could aid assessment. Routine monitoring of radiographic changes with serial spine radiographs is not recommended.

Conclusion. These recommendations provide updated guidance regarding use of new medications and imaging of the axial skeleton in the management of AS and nonradiographic axial SpA.

INTRODUCTION

Axial spondyloarthritis (SpA), comprising ankylosing spondylitis (AS) and nonradiographic axial SpA, is the main form of chronic inflammatory arthritis affecting the axial skeleton (1). AS affects 0.1–0.5% of the population, and is characterized by inflammatory back pain, radiographic sacroiliitis, excess spinal bone formation, and a high prevalence of HLA–B27 (2,3). Although nonradiographic axial SpA shares several features with AS, advanced sacroiliac joint damage and spine ankylosis are absent (4). The severity of arthralgia, stiffness, and limited flexibility varies widely among patients and over the course of axial SpA. Skeletal disease may be accompanied by uveitis, psoriasis, and inflammatory bowel disease (IBD). Axial SpA can impose substantial physical and social burdens on patients, and can interfere with work and schooling (5,6). The goals of treatment are to alleviate symptoms, improve functioning, maintain the ability to work, decrease disease complications, and forestall skeletal damage as much as possible.

In 2015, the American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) published recommendations for the treatment of adults with AS and those with nonradiographic axial SpA (7). Recommendations were provided for pharmacologic treatment, rehabilitation, use of surgery, management of selected comorbidities, disease monitoring, patient education, and preventive care. The recommendations were tailored to patients with either active or stable disease and focused on the most common decisions confronting clinicians when treating these patients.

The advent of new medications to treat axial SpA warranted this update. We did not reexamine all of the 2015 recommendations, but rather focused on those questions for which consequential new evidence was present. We added several new recommendations on how the newly available medications should fit in treatment strategies and on the use of imaging. The target populations are adults with AS or nonradiographic axial SpA. The target users of these recommendations are rheumatologists, primary care clinicians, physiatrists, physical therapists, and others providing care to patients with axial SpA.

METHODS

These recommendations followed ACR and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology (8,9), as described in Supplementary Appendix 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract. Briefly, systematic literature reviews were done for prespecified clinical population, intervention, comparator, outcomes (PICO) questions. The resulting evidence was reviewed, and recommendations formulated and voted on, by an expert voting panel (see Supplementary Appendices 2–5 at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Key definitions, including ones for active and stable disease, are provided in Table 1. Clinical trials of ixekizumab became available during the time the manuscript was in preparation, after the voting panel had met (10,11). The data from these trials were provided to the voting panel, and revised recommendations that included ixekizumab were reviewed and voted on by the panel.

This article is published simultaneously in *Arthritis Care & Research.*

The views expressed herein do not necessarily represent those of the National Institutes of Health or the United States Department of Veterans Affairs.

Supported by the American College of Rheumatology, the Spondylitis Association of America, and the Spondyloarthritis Research and Treatment Network. Dr. Ward's work was supported by the NIH (Intramural Research Program grant ZIA-AR-041153 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases).

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Submitted for publication March 28, 2019; accepted in revised form July 9, 2019.

Table 1. Definitions of key terms*

Term	Definition
Active disease	Disease causing symptoms at an unacceptably bothersome level to the patient and judged by the examining clinician to be due to inflammation.
Stable disease	Disease that was asymptomatic or causing symptoms but at an acceptable level as reported by the patient. A minimum of 6 months was required to qualify as clinically stable.
Primary nonresponse	Absence of a clinically meaningful improvement in disease activity over the 3 to 6 months after treatment initiation, not related to toxicity or poor adherence.
Secondary nonresponse	Recurrence of ankylosing spondylitis activity, not due to treatment interruption or poor adherence, after having a sustained clinically meaningful improvement on treatment (generally, beyond the initial 6 months of treatment).
Conventional synthetic antirheumatic drug	Sulfasalazine, methotrexate, leflunomide, apremilast, thalidomide, pamidronate.
Biosimilar	Biopharmaceuticals that are copies of an original biologic medication and tested to be of the same purity and potency as the original. In these recommendations, we refer only to TNFi biosimilars. Examples include infliximab-dyyb, etanercept-szzs, and adalimumab-atto.
TNFi	Infliximab, etanercept, adalimumab, certolizumab, golimumab, and their biosimilars.
TNFi monoclonal antibodies	Infliximab, adalimumab, certolizumab, golimumab.
Biologics	TNFi, abatacept, rituximab, sarilumab, tocilizumab, ustekinumab, secukinumab, ixekizumab.**
High-quality evidence	Studies that provide high confidence in the effect estimate, and new data from future studies are thought unlikely to change the effect.
Moderate-quality evidence	Studies that provide confidence that the true effect is likely to be close to the estimate but could be substantially different.
Low-quality evidence	Studies that provide limited confidence about the effect, and the true effect may be substantially different from the estimate.
Very low-quality evidence	Studies that provide very little certainty about the effect, and the true effect may be quite different from the estimate.
Strong recommendation	Action should be favored in almost all patients, usually requiring high-quality evidence, high confidence that future research will not alter the conclusion, AND an assessment that the desirable effects of the intervention outweigh the undesirable effects. Should not be taken to imply that the intervention has large clinical benefits.
Conditional recommendation	Action should be followed in only selected cases, often limited by low-quality evidence, OR when the desirable and undesirable consequences of an intervention are more balanced, OR if patients' preferences for the intervention are thought to vary widely.
Patient preferences	Beliefs and expectations regarding potential benefits and harms of treatment and how these relate to an individual's goals for health and life.
Shared decision-making	The process by which a patient and clinician arrive at an individualized treatment decision based on an understanding of the potential benefits and risks of available treatment options and of a patient's values and preferences.

* TNFi = tumor necrosis factor inhibitor.

RESULTS

Here we present the recommendations that were reviewed in this update, whether it was a new recommendation (designated "new") or reevaluation of an existing recommendation. Table 2 and Table 3 provide all current recommendations, including those from the 2015 report that were not newly reviewed. The order of recommendations presented here does not imply priority for use or recommended sequencing of different interventions. PICO numbers following each recommendation can be used to locate related evidence in Supplementary Appendix 6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract.

**Correction added on 26 September 2019, after first online publication: Secukinumab and ixekizumab were omitted in Table 1. They have been restored in this version of the article.

A. Recommendations for the treatment of patients with active AS

In adults with active AS, we conditionally recommend continuous treatment with nonsteroidal antiinflammatory drugs (NSAIDs) over on-demand treatment with NSAIDs (PICO 1).

The efficacy of NSAIDs for symptom improvement in active AS has been established in many controlled trials. Evidence that continuous NSAID use results in slower rates of spinal fusion on radiographs over 2 years compared to on-demand NSAID use is inconsistent, with results of one trial of celecoxib suggesting less progression with continuous use, and one trial of diclofenac indicating no difference in progression (12,13) (See Supplementary Appendix 6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Despite the

Table 2. Recommendations for the treatment of adults with AS*

Recommendation	Level of evidence	PICO
RECOMMENDATIONS FOR ADULTS WITH ACTIVE AS		
1. We strongly recommend treatment with NSAIDs over no treatment with NSAIDs.†	Low	2
2. We conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs.	Low to moderate	1
3. We do not recommend any particular NSAID as the preferred choice.†	Low to moderate	3
4. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications. Sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNFi are not available.	Very low to moderate	7
5. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib.	Very low	60
6. In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi.	High	6
7. We do not recommend any particular TNFi as the preferred choice.	Moderate	5
8. In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab.	High	58
9. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab.	Very low	59
10. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib.	Very low	61
11. In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib.	Low	8
12. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with a different TNFi in patients with primary nonresponse to TNFi.	Very low	10
13. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with a different TNFi over treatment with a non-TNFi biologic in patients with secondary nonresponse to TNFi.	Very low	10
14. In adults with active AS despite treatment with the first TNFi used, we strongly recommend against switching to treatment with a biosimilar of the first TNFi.	Very low	62
15. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of treatment with a new biologic.	Very low	9
16. We strongly recommend against treatment with systemic glucocorticoids.†	Very low	4
17. In adults with isolated active sacroiliitis despite treatment with NSAIDs, we conditionally recommend treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.†	Very low	13
18. In adults with stable axial disease and active enthesitis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided.†	Very low	14
19. In adults with stable axial disease and active peripheral arthritis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.†	Very low	15
20. We strongly recommend treatment with physical therapy over no treatment with physical therapy.†	Moderate	16
21. We conditionally recommend active physical therapy interventions (supervised exercise) over passive physical therapy interventions (massage, ultrasound, heat).†	Very low	17
22. We conditionally recommend land-based physical therapy interventions over aquatic therapy interventions.†	Moderate	18
RECOMMENDATIONS FOR ADULTS WITH STABLE AS		
23. We conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs.	Low to moderate	1
24. In adults receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone compared to continuing both treatments.	Very low	11
25. In adults receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing both treatments.	Very low	12
26. In adults receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic.	Very low to low	66

(Continued)

Table 2. (*Cont'd*)

Recommendation	Level of evidence	PICO
27. In adults receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach.	Very low to low	65
28. In adults receiving treatment with an originator TNFi, we strongly recommend continuing treatment with the originator TNFi over mandated switching to its biosimilar.	Very low	63
29. We strongly recommend treatment with physical therapy over no treatment with physical therapy.†	Low	19
RECOMMENDATIONS FOR ADULTS WITH ACTIVE OR STABLE AS		
30. In adults receiving treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate.	Low	64
31. We conditionally recommend advising unsupervised back exercises.†	Moderate	20
32. We conditionally recommend fall evaluation and counseling.†	Very low	51
33. We conditionally recommend participation in formal group or individual self-management education.†	Moderate	48
34. In adults with spinal fusion or advanced spinal osteoporosis, we strongly recommend against treatment with spinal manipulation.†	Very low	21
35. In adults with advanced hip arthritis, we strongly recommend treatment with total hip arthroplasty over no surgery.†	Very low	25
36. In adults with severe kyphosis, we conditionally recommend against elective spinal osteotomy.†	Very low	26
RECOMMENDATIONS FOR ADULTS WITH AS-RELATED COMORBIDITIES		
37. In adults with acute iritis, we strongly recommend treatment by an ophthalmologist to decrease the severity, duration, or complications of episodes.†	Very low	27
38. In adults with recurrent iritis, we conditionally recommend prescription of topical glucocorticoids over no prescription for prompt at-home use in the event of eye symptoms to decrease the severity or duration of iritis episodes.†	Very low	28
39. In adults with recurrent iritis, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics.	Low	29
40. In adults with inflammatory bowel disease, we do not recommend any particular NSAID as the preferred choice to decrease the risk of worsening of inflammatory bowel disease symptoms.†	Very low	31
41. In adults with inflammatory bowel disease, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics.	Very low	32
DISEASE ACTIVITY ASSESSMENT, IMAGING, AND SCREENING		
42. We conditionally recommend the regular-interval use and monitoring of a validated AS disease activity measure.†	Very low	54
43. We conditionally recommend regular-interval use and monitoring of CRP concentrations or ESR over usual care without regular CRP or ESR monitoring.†	Very low	55
44. In adults with active AS, we conditionally recommend against using a treat-to-target strategy using a target of ASDAS <1.3 (or 2.1) over a treatment strategy based on physician assessment.	Low	67
45. We conditionally recommend screening for osteopenia/osteoporosis with DXA scan over no screening.†	Very low	49
46. In adults with syndesmophytes or spinal fusion, we conditionally recommend screening for osteoporosis/osteopenia with DXA scan of the spine as well as the hips, compared to DXA scan solely of the hip or other non-spine sites.†	Very low	50
47. We strongly recommend against screening for cardiac conduction defects with electrocardiograms.†	Very low	52
48. We strongly recommend against screening for valvular heart disease with echocardiograms.†	Very low	53
49. In adults with AS of unclear activity while on a biologic, we conditionally recommend obtaining a spinal or pelvis MRI to assess activity.	Very low	68
50. In adults with stable AS, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity.	Very low	69
51. In adults with active or stable AS on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach.	Very low	70

* AS = ankylosing spondylitis; PICO = population, intervention, comparison, and outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; TNFi = tumor necrosis factor inhibitor; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ASDAS = Ankylosing Spondylitis Disease Activity Score; DXA = dual x-ray absorptiometry; MRI = magnetic resonance imaging.
† These recommendations were from 2015 and were not reviewed in this update. The number preceding the recommendation is the recommendation number and is referenced as bracketed numbers in Figure 1.

Table 3. Recommendations for the treatment of adults with nonradiographic axial SpA*

Recommendation	Level of evidence	PICO
RECOMMENDATIONS FOR ADULTS WITH ACTIVE NONRADIOGRAPHIC AXIAL SpA		
52. We strongly recommend treatment with NSAIDs over no treatment with NSAIDs.†	Very low	34
53. We conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs.	Very low	33
54. We do not recommend any particular NSAID as the preferred choice.†	Very low	35
55. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications.	Very low	39
56. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi.	High	38
57. We do not recommend any particular TNFi as the preferred choice.	Very low	37
58. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib.	Very low	73
59. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab.	Very low	71
60. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab.	Very low	72
61. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib.	Very low	74
62. In adults with active nonradiographic axial SpA despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib.	Very low	40
63. In adults with active nonradiographic axial SpA and primary nonresponse to the first TNFi used, we conditionally recommend switching to secukinumab or ixekizumab over switching to a different TNFi.	Very low	42
64. In adults with active nonradiographic axial SpA and secondary nonresponse to the first TNFi used, we conditionally recommend switching to a different TNFi over switching to a non-TNFi biologic.	Very low	42
65. In adults with active nonradiographic axial SpA despite treatment with the first TNFi used, we strongly recommend against switching to the biosimilar of the first TNFi.	Very low	75
66. In adults with active nonradiographic axial SpA despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of treatment with a different biologic.	Very low	41
67. We strongly recommend against treatment with systemic glucocorticoids.†	Very low	36
68. In adults with isolated active sacroiliitis despite treatment with NSAIDs, we conditionally recommend treatment with local glucocorticoids over no treatment with local glucocorticoids.†	Very low	45
69. In adults with active enthesitis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided.†	Very low	46
70. In adults with active peripheral arthritis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.†	Very low	47
71. We strongly recommend treatment with physical therapy over no treatment with physical therapy.†	Low	22
72. We conditionally recommend active physical therapy interventions (supervised exercise) over passive physical therapy interventions (massage, ultrasound, heat).†	Very low	23
73. We conditionally recommend land-based physical therapy interventions over aquatic therapy interventions.†	Very low	24
RECOMMENDATIONS FOR ADULTS WITH STABLE NONRADIOGRAPHIC AXIAL SpA		
74. We conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs.	Very low	33
75. In adults receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone compared to continuing both medications.	Very low	43
76. In adults receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing treatment with both medications.	Very low	44
77. In adults receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic.	Low	79
78. In adults receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach.	Very low	78
79. In adults receiving treatment with an originator TNFi, we strongly recommend continuation of treatment with the originator TNFi over mandated switching to its biosimilar.	Very low	76

(Continued)

Table 3. (*Cont'd*)

Recommendation	Level of evidence	PICO
RECOMMENDATIONS FOR ADULTS WITH ACTIVE OR STABLE NONRADIOGRAPHIC AXIAL SpA		
80. In adults receiving treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate.	Low	77
DISEASE ACTIVITY ASSESSMENT AND IMAGING		
81. We conditionally recommend the regular-interval use and monitoring of a validated AS disease activity measure.†	Very low	56
82. We conditionally recommend regular-interval use and monitoring of the CRP concentrations or ESR over usual care without regular CRP or ESR monitoring.†	Very low	57
83. In adults with active nonradiographic axial SpA, we conditionally recommend against using a treat-to-target strategy using a target of ASDAS <1.3 (or 2.1) over a treatment strategy based on physician assessment.	Very low	80
84. In adults with nonradiographic axial SpA of unclear activity while on a biologic, we conditionally recommend obtaining a pelvis MRI to assess activity.	Very low	81
85. In adults with stable nonradiographic axial SpA, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity.	Very low	82
86. In adults with active or stable nonradiographic axial SpA on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach.	Very low	83

* SpA = spondyloarthritis; PICO = population, intervention, comparison, and outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; TNFi = tumor necrosis factor inhibitor; AS = ankylosing spondylitis; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ASDAS = Ankylosing Spondylitis Disease Activity Score; MRI = magnetic resonance imaging.
† These recommendations were from 2015 and were not reviewed in this update. The number preceding the recommendation is the recommendation number and is referenced as bracketed numbers in Figure 1.

uncertainty regarding potential disease-modifying effects, the committee conditionally favored continuous use of NSAIDs in patients with active AS, primarily for controlling disease activity. The decision to use NSAIDs continuously may vary depending on the severity of symptoms, patient preferences, and comorbidities, particularly gastrointestinal and kidney comorbidities, and cardiovascular disease.

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications (new, PICO 7). Sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when tumor necrosis factor inhibitors (TNFi) are not available.

Treatment with sulfasalazine is recommended primarily for patients with prominent peripheral arthritis and few or no axial symptoms. However, TNFi may provide a better option for these patients. Evidence for the efficacy of sulfasalazine is based on 8 older controlled trials that showed benefit for peripheral arthritis (see Supplementary Appendix 6, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Although a recent placebo-controlled trial of sulfasalazine demonstrated improvement in axial symptoms, and modest clinical and imaging responses were seen in a second trial, the preponderance of evidence indicates that sulfasalazine has little benefit for axial symptoms (14,15). Sulfasalazine may have a role in treating patients who have contraindications to TNFi, those who decline treatment with TNFi, or those with limited access to TNFi.

Three trials of methotrexate with negative results tested doses of ≤10 mg weekly, and the lack of benefit may reflect the low doses used (16–18). One uncontrolled study of methotrexate 20 mg weekly showed no improvement in axial symptoms, but a decrease in swollen joint count (19). Treatment with methotrexate may be considered for patients with predominately peripheral arthritis, although among nonbiologics, there is more evidence supporting the use of sulfasalazine.

A phase II study of tofacitinib showed benefit in both clinical and imaging outcomes of axial disease over 12 weeks (20). Use of tofacitinib could be another option, although the results of phase III trials are not available. Leflunomide, apremilast, thalidomide, and pamidronate are not recommended (See Supplementary Appendix 6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract).

In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi (PICO 6).

In adults with active AS despite treatment with NSAIDs, we do not recommend any particular TNFi as the preferred choice (PICO 5).

The efficacy of TNFi in patients with active AS has been demonstrated in 24 randomized controlled trials, most of which were short-term (6 months or shorter) placebo-controlled studies. Improvements were shown in patient-reported outcomes, composite response criteria, and spine and sacroiliac inflammation on magnetic resonance imaging (MRI) (see Supplementary Appendix 6, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). The panel judged that the evidence justified a strong recommenda-

tion for use of TNFi in patients whose AS remained active (as defined in Table 1) despite treatment with NSAIDs. The panel recommended that lack of response (or intolerance) to at least 2 different NSAIDs at maximal doses over 1 month, or incomplete responses to at least 2 different NSAIDs over 2 months, would be adequate trials with which to judge NSAID responsiveness prior to escalating to treatment with TNFi.

Indirect comparisons in network meta-analyses of clinical trials have not showed clinically meaningful differences in short-term efficacy among TNFi in the treatment of active AS (see Supplementary Appendix 6, at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract) (21). Direct comparisons among these medications are limited to a trial of infliximab versus its biosimilar, and a very small open-label trial of infliximab versus etanercept (22,23). The panel judged that the evidence did not support preference of 1 TNFi over any other for the typical patient. Important exceptions apply to patients with recurrent uveitis or coexistent IBD (see PICO 29 and PICO 32 below). Patients treated with infliximab may have increased risks of tuberculosis and of infections generally (24,25). TNFi other than infliximab should be considered for patients at higher risk of tuberculosis exposure (either through travel or household contacts) or with a history of recurrent infections. Patient preferences regarding the frequency of dosing and route of administration should be weighed when selecting a specific TNFi.

In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab (new, PICO 58).

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab (new, PICO 59).

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib (new, PICO 60).

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib (new, PICO 61).

The use of secukinumab and ixekizumab in patients with active AS is supported by data from large placebo-controlled trials (see Supplementary Appendix 6, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). The panel recommended use of TNFi over secukinumab or ixekizumab based on greater experience with TNFi and familiarity with their long-term safety and toxicity. Similarly, the panel judged that TNFi, secukinumab, or ixekizumab should be used over tofacitinib, given the larger evidence base for TNFi, secukinumab, and ixekizumab. In patients with coexisting ulcerative colitis, if treatment with TNFi is not an option, tofacitinib should be considered over secukinumab or ixekizumab. Interleukin-17 (IL-17) inhibitors have not been shown to be efficacious in IBD, although tofacitinib is an approved treatment for ulcerative colitis (26,27).

In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib (new, PICO 8).

No studies have directly compared the risks and benefits of treatment alternatives in patients who have contraindications to treatment with TNFi. The panel favored treatment with secukinumab or ixekizumab over treatment with sulfasalazine or methotrexate based on a higher likelihood of benefit, but this recommendation was conditional on the specific contraindication. If the contraindication to TNFi use was the presence of congestive heart failure or demyelinating disease, secukinumab or ixekizumab was preferred, since these medications have not been shown to worsen these conditions. If the contraindication to TNFi use was tuberculosis, other chronic infection, or a high risk of recurrent infections, sulfasalazine was preferred over secukinumab, izekizumab, and tofacitinib. In these cases, efforts to mitigate the infections should be undertaken so that TNFi might safely be used. Treatment with rituximab, abatacept, ustekinumab, or IL-6 inhibitors is not recommended, even in patients with contraindications to TNFi, due to lack of effectiveness.

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with a different TNFi in patients with primary nonresponse to TNFi (new, PICO 10).

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with a different TNFi over treatment with a non-TNFi biologic in patients with secondary nonresponse to TNFi (new, PICO 10).

In adults with active AS despite treatment with the first TNFi used, we strongly recommend against switching to treatment with a biosimilar of the first TNFi (new, PICO 62).

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of switching to a new biologic (PICO 9).

Direct comparisons of treatment strategies for patients who do not have or sustain adequate responses to their first TNFi have not been reported, and the recommendations are based on the panel's consideration of indirect comparisons among the available treatment options (see Supplementary Appendix 6, at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Data from observational studies suggest that 25–40% of patients who switch from one TNFi to another will have a meaningful response (e.g.,

50% improvement in Bath AS Disease Activity Index) to the second TNFi (28–30). However, not all patients in these studies switched TNFi because of ineffectiveness.

The panel judged that treatment should differ for patients who had a primary nonresponse to TNFi and those with secondary nonresponse to TNFi. Switching to secukinumab or ixekizumab was recommended in most patients who had a primary nonresponse to the first TNFi, under the assumption that TNF was not the key inflammatory mediator in these patients. Continuing treatment with the first TNFi could be considered if additional time was believed important to assess the response fully, or if a higher dose or shorter dosing interval was thought to be beneficial.

In patients who relapse after an initial response (i.e., secondary nonresponse), the panel judged that treatment with a different TNFi held a reasonable prospect of benefit and should be used in most patients, rather than immediately switching to a different class of biologics. Although ixekizumab is efficacious among TNFi nonresponders, trials have not directly compared responses to ixekizumab (or secukinumab) to responses to a second TNFi in patients with a secondary nonresponse to the first TNFi (11). Given that options for biologics are limited, treatment with a second TNFi was recommended in these patients.

In cases of nonresponse (primary or secondary), the panel recommended against switching to the biosimilar of the first TNFi (e.g., switching from originator infliximab to infliximab-dyyb), as the clinical response would not be expected to be different. The panel also recommended against the addition of sulfasalazine or methotrexate to TNFi in cases of nonresponse to TNFi, judging any benefit would likely be marginal. The addition of sulfasalazine could be considered in the rare patient whose axial symptoms are well-controlled with TNFi but who has active peripheral arthritis.

In adults with either active or stable AS on treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate (new, PICO 64).

In rheumatoid arthritis, the likelihood of TNFi discontinuation is lower among patients who receive co-treatment with methotrexate, perhaps by reducing the development of antidrug antibodies (31). In AS, it is less clear whether the duration of TNFi use, and by inference their effectiveness, is similarly prolonged (32). Data from observational studies are conflicting, although some studies, primarily of infliximab, showed longer TNFi treatment when methotrexate was co-administered (see Supplementary Appendix 6 at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Clinical responses were not greater among patients who received co-treatment with methotrexate. In the absence of convincing evidence of benefit, and due to greater burden for patients, the panel recommended against routine co-administration of methotrexate with TNFi, although its use could be considered in patients treated with infliximab.

B. Recommendations for the treatment of patients with stable AS

In adults with stable AS, we conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs (PICO 1).

This recommendation applies to patients whose AS has been stable while not receiving any pharmacologic treatment. In this group, the panel considered that the potential toxicities of continuous NSAID treatment outweighed the uncertain benefit of less radiographic progression. On-demand treatment should be considered for short-term symptom recurrences (flares).

In adults with stable AS receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone over continuing both medications (PICO 11).

In adults with stable AS receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing both medications (PICO 12).

No new studies have directly compared outcomes between patients who continued combination treatment and those who discontinued either NSAIDs or a conventional synthetic antirheumatic drug (csARD). The NSAID-sparing potential of etanercept was demonstrated in a recent trial (33). The panel judged these recommendations primarily based on symptom control, rather than on any potential effect of combination therapy on future spinal fusion. In stable patients, a trial of withdrawing either the NSAIDs or the csARD should be considered, due to the likelihood of greater toxicity with the long-term use of more than one medication. However, on-demand NSAID treatment for control of intermittent symptoms is recommended for patients with good responses to previous courses of NSAIDs.

In adults with stable AS receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic (new, PICO 66).

In adults with stable AS receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach (new, PICO 65).

Data from several observational studies suggest that discontinuation of TNFi after achieving either remission or low disease activity results in relapses in 60–74% of patients, occasionally within a few weeks to months from discontinuation (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Although the data only concerned TNFi discontinuation, the panel judged that a similar recommendation would also apply to other biologics. In general, treatment with a biologic should be planned to be

continued long-term, barring toxicities. Discontinuation might be considered in patients in sustained remission (i.e., several years), with the anticipation that only one-third of patients would not experience relapse. Patient preferences should help guide this decision.

Tapering of TNFi could entail a change in either the dose or frequency of administration. Two controlled unblinded trials of tapering etanercept to 25 mg weekly versus maintaining the dose at 50 mg weekly in patients with stable AS showed that remission or partial remission was somewhat less likely among those in whom etanercept was tapered (34,35). In small observational studies, 53–70% of patients were still receiving their reduced dose at 2 years, but there is little evidence regarding maintenance of long-term remission after tapering of TNFi (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Therefore, the panel recommended against tapering of biologics as a standard approach. One condition in which tapering could be considered would be in patients with prolonged stable AS, if the patient and provider engage in shared decision-making.

In adults with stable AS receiving an originator TNFi, we strongly recommend continuing treatment with the originator TNFi over mandated switching to its biosimilar (new, PICO 63).

While the efficacy of originator and biosimilar TNFi is comparable, and although either could be chosen to initiate new courses of TNFi treatment, it was the opinion of the panel to recommend against mandated switching to a biosimilar during the course of treatment, in the absence of evidence of interchangability. Medication changes can increase the risk of destabilizing a patient's condition, and the panel judged that additional data were needed to understand the frequency of potential problems and concerns associated with switching patients who were stable on an originator TNFi to its biosimilar. Given these concerns, the panel judged that there should be a compelling rationale for switching medications, particularly in light of the marginal cost savings apparent for US patients (36).

C. Recommendations for adults with AS-related comorbidities

In adults with AS and recurrent uveitis, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics (PICO 29).

Evidence for this recommendation is limited to indirect comparisons of the rates of acute uveitis episodes in clinical trials or observational studies, rather than from direct comparisons (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Many reports showed overall rates of uveitis without separately reporting recurrences as opposed to incident episodes (37). The rates were generally lower for adalimumab and infliximab compared to etanercept. For example, a large observational study demonstrated rates of uveitis (per 100 patient-years) in patients receiving adalimumab, infliximab, and etanercept of 13.6, 27.5, and 60.3, respectively, compared to pretreatment rates of 36.8, 45.5, and 41.6, respectively (38). Adalimumab or infliximab are preferred over etanercept for the treatment of AS in patients with recurrent uveitis. Certolizumab or golimumab may also be considered, although supporting data are less substantial (39,40). Data from clinical trials suggest that rates of uveitis flares were not different between patients with AS treated with secukinumab and those treated with placebo, but more evidence is needed. Secukinumab was not efficacious in the treatment of panuveitis or posterior uveitis (41). Rates of uveitis flares among patients treated with ixekizumab have not been well-defined.

In adults with AS and IBD, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics (PICO 32).

This recommendation was based on limited indirect evidence on the risks of flares or new onset of IBD among patients with AS during treatment with biologics, and the much larger literature on the treatment of IBD in general. Patients with AS treated with infliximab or adalimumab have lower risks of IBD exacerbations than those treated with etanercept (see Supplementary Appendix 6, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). Infliximab, adalimumab, and certolizumab are approved for the treatment of Crohn's disease, and infliximab, adalimumab, and golimumab are approved for the treatment of ulcerative colitis, while etanercept is not approved for either condition (42,43). This evidence is the basis for the recommendation favoring TNFi monoclonal antibody use in patients with AS and coexisting IBD. The choice of the particular TNFi monoclonal antibody should be made in consultation with the patient's gastroenterologist. Secukinumab has been associated with the new onset, or exacerbation, of Crohn's disease (44–46). Increased risks of IBD exacerbation appear to also occur with ixekizumab (47).

D. Recommendations for the treatment of patients with either active or stable nonradiographic axial spondyloarthritis

Parallel questions on pharmacologic treatment were investigated for patients with nonradiographic axial SpA. There were no relevant published data for 19 questions. There was high-quality evidence only for the use of TNFi in nonradiographic axial SpA, which was examined in several clinical trials. Low-quality or very low-quality evidence from single studies suggested no differences in outcomes among different TNFi in nonradiographic axial SpA, high likelihood of relapse following discontinuation of TNFi, and no association between co-treatment with nonbiologics and TNFi persistence (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract).

Therefore, the recommendations for nonradiographic axial SpA were largely extrapolated from evidence in AS (Table 3). The recommendations were identical in both patient groups with 1 notable exception: treatment with secukinumab or ixekizumab was strongly recommended over no treatment with secukinumab or ixekizumab in patients with AS, while use of these medications was conditionally recommended in patients with nonradiographic axial SPA, because trials in nonradiographic axial SPA have not been reported. Evidence on tofacitinib in nonradiographic axial SpA has not been reported.

E. Disease activity assessment and imaging

In adults with active AS, we conditionally recommend against using the treat-to-target strategy, which aims at a target of an Ankylosing Spondylitis Disease Activity Score <1.3 (or 2.1), over a treatment strategy based on physician assessment (new, PICO 67).

The concept of treat-to-target strategies is well-founded in chronic disease management for conditions that have an accurate measure of disease activity (often one that is asymptomatic, as in blood pressure or glycosylated hemoglobin), a tight link between this disease activity measure and future health outcomes, and evidence that maintaining a particular target in the disease activity measure is closely associated with better long-term health (48). The treat-to-target approach in AS is indirectly supported by associations between levels of AS activity and future radiographic progression but lacks robust direct evidence. Because adoption of this strategy would place additional burdens on patients and providers, the panel judged that more convincing evidence of benefit should be present before endorsing this change in practice. There was also concern that focus on a specific target could lead to rapid cycling through all currently available treatments in some patients. As reflected in the 2015 guidelines, quantifying disease activity is important to help guide treatment decisions.

In adults with AS of unclear activity while receiving a biologic, we conditionally recommend obtaining a spinal or pelvis MRI to assess activity (new, PICO 68).

In adults with nonradiographic axial SpA of unclear activity while receiving a biologic, we conditionally recommend obtaining a pelvis MRI to assess activity (new, PICO 81).

Because physical and laboratory measures are often normal despite active axial SpA, and because symptoms may be nonspecific, it may be difficult to know whether a patient is experiencing inflammation that warrants a change in treatment. Limited evidence suggests that knowledge of MRI findings in the spine and sacroiliac joints may alter treatment recommendations. However, the degree of inflammatory change on MRI may not correlate with treatment responses, and the location of inflammation on MRI may not correlate with the location of pain (49) (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). The panel judged that MRI could provide useful information in cases where the level of disease activity was unclear and where this information would influence treatment decisions. For patients with nonradiographic axial SpA, the imaging should focus on the sacroiliac joints. In interpreting MRI results, it is important to keep in mind the range and frequency of abnormalities, including bone marrow edema lesions, that may occur in individuals without axial SpA and that may not represent inflammation due to axial SpA (50,51). MRI is not recommended in patients in whom disease activity is either clearly clinically active or clinically stable, or when the results of MRI would not be expected to change treatment.

In adults with stable AS, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity (new, PICO 69).

In adults with stable nonradiographic axial SpA, we conditionally recommend against obtaining a spine or pelvis MRI to confirm inactivity (new, PICO 82).

Because the clinical assessment of inflammation in axial SpA has many limitations, questions may arise about whether subclinical inflammation that could be detected by MRI is being "missed" by either the physical examination, symptoms, or laboratory studies. Given the lack of evidence that obtaining an MRI in stable patients improves clinical outcomes, the only moderate sensitivity and specificity of MRI-defined abnormalities for measurement of activity in axial SpA, the burden of testing, and concern for possible overtreatment, the panel recommended against obtaining an MRI in this setting. MRI could be considered in circumstances where the clinician and patient differ in their assessment of whether the disease is stable.

In adults with active or stable AS receiving any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach (new, PICO 70).

In adults with active or stable nonradiographic axial SpA on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach (new, PICO 83).

Spine radiographs are useful for the diagnosis of axial SpA, in evaluating the extent of spinal fusion, and for investigating new spinal pain in patients with established AS. In research studies, small changes in the extent of spine damage can be detected in 20–35% of patients with AS over a 2-year interval (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.41042/abstract). There is no evidence that monitoring serial changes in

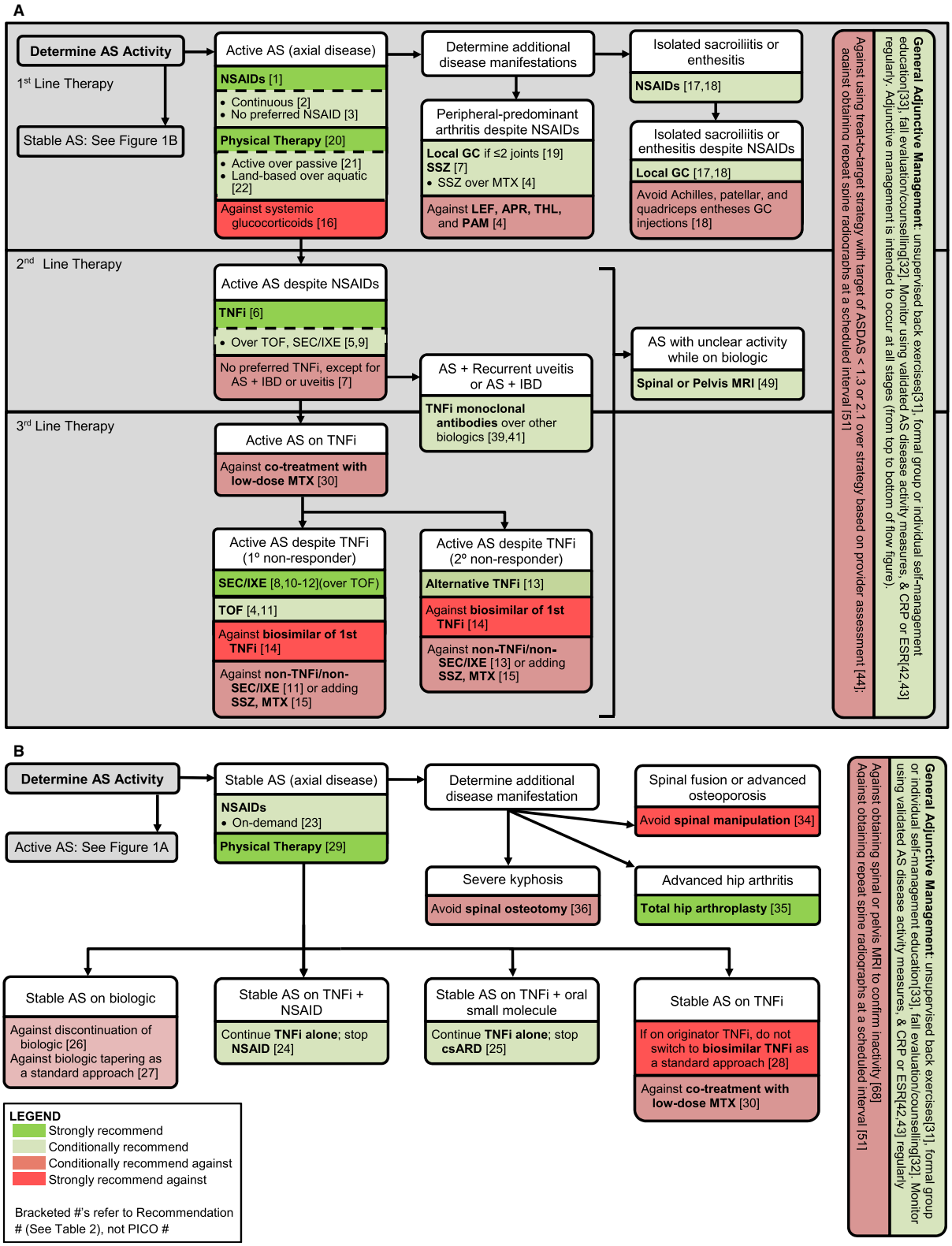
A
Determine AS Activity
1st Line Therapy
Stable AS: See Figure 1B
Active AS (axial disease)
NSAIDs [1]
• Continuous [2]
• No preferred NSAID [3]
Physical Therapy [20]
• Active over passive [21]
• Land-based over aquatic [22]
Against systemic glucocorticoids [16]
Determine additional disease manifestations
Peripheral-predominant arthritis despite NSAIDs
Local GC if ≤2 joints [19]
SSZ [7]
• SSZ over MTX [4]
Against LEF, APR, THL, and PAM [4]
Isolated sacroiliitis or enthesitis
NSAIDs [17,18]
Isolated sacroiliitis or enthesitis despite NSAIDs
Local GC [17,18]
Avoid Achilles, patellar, and quadriceps entheses GC injections [18]
2nd Line Therapy
Active AS despite NSAIDs
TNFi [6]
• Over TOF, SEC/IXE [5,9]
No preferred TNFi, except for AS + IBD or uveitis [7]
AS + Recurrent uveitis or AS + IBD
TNFi monoclonal antibodies over other biologics [39,41]
AS with unclear activity while on biologic
Spinal or Pelvis MRI [49]
3rd Line Therapy
Active AS on TNFi
Against co-treatment with low-dose MTX [30]
Active AS despite TNFi (1° non-responder)
SEC/IXE [8,10-12](over TOF)
TOF [4,11]
Against biosimilar of 1st TNFi [14]
Against non-TNFi/non-SEC/IXE [11] or adding SSZ, MTX [15]
Active AS despite TNFi (2° non-responder)
Alternative TNFi [13]
Against biosimilar of 1st TNFi [14]
Against non-TNFi/non-SEC/IXE [13] or adding SSZ, MTX [15]
General Adjunctive Management: unsupervised back exercises[31], formal group or individual self-management education[33], fall evaluation/counselling[32]. Monitor using validated AS disease activity measures, & CRP or ESR[42,43] regularly. Adjunctive management is intended to occur at all stages (from top to bottom of flow figure).
Against using treat-to-target strategy with target of ASDAS < 1.3 or 2.1 over strategy based on provider assessment [44]; against obtaining repeat spine radiographs at a scheduled interval [51]
B
Determine AS Activity
Active AS: See Figure 1A
Stable AS (axial disease)
NSAIDs
• On-demand [23]
Physical Therapy [29]
Determine additional disease manifestation
Spinal fusion or advanced osteoporosis
Avoid spinal manipulation [34]
Severe kyphosis
Avoid spinal osteotomy [36]
Advanced hip arthritis
Total hip arthroplasty [35]
Stable AS on biologic
Against discontinuation of biologic [26]
Against biologic tapering as a standard approach [27]
Stable AS on TNFi + NSAID
Continue TNFi alone; stop NSAID [24]
Stable AS on TNFi + oral small molecule
Continue TNFi alone; stop csARD [25]
Stable AS on TNFi
If on originator TNFi, do not switch to biosimilar TNFi as a standard approach [28]
Against co-treatment with low-dose MTX [30]
LEGEND
Strongly recommend
Conditionally recommend
Conditionally recommend against
Strongly recommend against
Bracketed #'s refer to Recommendation # (See Table 2), not PICO #
General Adjunctive Management: unsupervised back exercises[31], formal group or individual self-management education[33], fall evaluation/counselling[32]. Monitor using validated AS disease activity measures, & CRP or ESR[42,43] regularly
Against obtaining spinal or pelvis MRI to confirm inactivity [68]
Against obtaining repeat spine radiographs at a scheduled interval [51]

Figure 1. Summary of the main recommendations for the treatment of patients with **A,** active ankylosing spondylitis and **B,** stable ankylosing spondylitis. AS = ankylosing spondylitis; NSAIDs = nonsteroidal antiinflammatory drugs; GC = glucocorticoid; SSZ = sulfasalazine; MTX = methotrexate; LEF = leflunomide; APR = apremilast; THL = thalidomide; PAM = pamidronate; TNFi = tumor necrosis factor inhibitor; TOF = tofacitinib; SEC = secukinumab; IXE = ixekizumab; IBD = inflammatory bowel disease; csARD = conventional synthetic antirheumatic drugs; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein level; ASDAS = Ankylosing Spondylitis Disease Activity Score; MRI = magnetic resonance imaging; PICO = population, intervention, comparison, and outcomes.

spine radiographs at a regular interval leads to better patient outcomes, and data balancing a clinical benefit with the risk of radiation exposure are absent. Therefore, the panel recommended against repeating spine radiographs as a standard approach. In the absence of clinical indications, repeat spine radiographs could be considered on an ad hoc basis for counseling patients on the progression of their disease, which may help in career and life planning.

F. Summary of recommendations

Figure 1 presents a diagram of the main treatment recommendations for active and stable AS, integrating the new recommendations with the 2015 recommendations that were not updated in this review.

DISCUSSION

This update was primarily motivated by the availability of new treatment options, notably secukinumab, ixekizumab, tofacitinib, and TNFi biosimilars, for patients with axial SpA. Providers and patients have questions on where these new medications fit in the pharmacologic strategy, and how originator TNFi, sulfasalazine, and NSAIDs should be used given these new options. Based on the current evidence and the considerations of the panel, NSAIDs and TNFi remain the primary classes of medications for the treatment of AS and nonradiographic axial SpA. Secukinumab or ixekizumab is recommended for patients with active disease who have heart failure or demyelinating disease as a contraindication to TNFi, and in primary nonresponders to TNFi. Secukinumab and ixekizumab are not recommended in patients with IBD or recurrent uveitis, as TNFi monoclonal antibodies are better options. Tofacitinib is a potential second-line option for patients with contraindications to TNFi other than infections. Recommendations regarding tofacitinib may change pending the results of larger clinical trials.

Several of the 2015 recommendations were modified in this update. The current recommendation is conditionally in favor of use of sulfasalazine in limited clinical circumstances, whereas the 2015 recommendations had this as an exception to the general recommendation against the use of conventional synthetic antirheumatic drugs. In the 2015 recommendations, sulfasalazine and pamidronate were suggested as alternatives for the treatment of patients with active disease and contraindications to TNFi, while the current recommendations suggest use of secukinumab or ixekizumab in most of these cases (except patients with high risk of infections). In cases of failure of TNFi, the 2015 guidelines included a conditional recommendation for a trial of a second TNFi and against use of a non-TNFi biologic, whereas the current guidelines differentiate treatment recommendations based on whether there was primary or secondary nonresponse to the TNFi. For the treatment of patients with recurrent uveitis, the previous guidelines specified conditional use of infliximab or adalimumab, while the update broadened this recommendation to include TNFi monoclonal antibodies generally. Similarly, for patients with coexisting IBD, the update includes a conditional recommendation for TNFi monoclonal antibodies over other biologics, rather than over only etanercept. Finally, the recommendation for use of TNFi in patients with active nonradiographic axial SpA was changed from conditional to strong.

New questions on the treatment of patients with stable disease were addressed in this update. Discontinuation of biologics is not recommended due to the likelihood for symptom recurrence. If tapering is considered, patients should be counseled regarding the potential for increased disease activity. Co-treatment with low-dose methotrexate is not generally recommended, but ongoing studies will shed further light on this question. Switching to a biosimilar during the course of treatment with TNFi is also not recommended, echoing the concerns previously expressed by the ACR (52).

Imaging remains a central tool in the diagnosis of axial SpA, but its role in monitoring patients is less well-defined. Spine and/or pelvis MRI could aid in the evaluation of patients in whom the degree of active inflammation is uncertain, and especially in those for whom the findings would change management. MRI is not recommended to seek subclinical inflammation in patients with stable disease (as defined in Table 1). However, MRI could be considered in circumstances where it may inform shared decision-making. We recommend against obtaining spine radiographs on scheduled intervals to monitor progression. This practice entails radiation exposure and would not alter treatment in most cases.

We used the GRADE method to develop these treatment recommendations in a way that was transparent, systematic, and explicit, and that was informed by the medical evidence as well as patient preferences. The major limitation of these guidelines is the very low quality of evidence for many recommendations, which necessitated reliance on the clinical expertise of the panel. For nonradiographic axial SpA, most recommendations were based on extrapolation of results from studies in AS. We tried to identify the most common and consequential treatment questions, so that the recommendations would be useful in guiding clinical decision-making. The low quality of evidence for many questions is an indication that research has not yet tackled many of the most important treatment questions. As more treatment options become available, this problem will grow. Importantly, failure to recommend a particular medication does not imply that it is contraindicated. Key evidence gaps include the comparative effectiveness and safety of different biologics, the optimal sequencing of treatments, and the role of NSAIDs.

This update addressed only a subset of treatment questions. The 2015 recommendations that were not reexamined are to be considered extant. Recommendations are meant to describe the approach to treatment of the typical patient and cannot anticipate all possible clinical scenarios. Application of these recommendations must be individualized, and requires

careful assessment, sound clinical judgment of each patient's circumstances, and consideration of a patient's preferences.

ACKNOWLEDGMENTS

We thank Cassie Shafer and Elin Aslanyan of the SAA for their partnership on this project. We thank SPARTAN for its partnership on this project. We thank our patient representatives for adding valuable perspectives. We thank the ACR staff, including Ms Regina Parker for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, and Ms Robin Lane for assistance in manuscript preparation. We thank Ms Janet Waters for help in developing the literature search strategy and performing the literature search and updates, and Ms Janet Joyce for peer-reviewing the literature search strategy.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ward had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ward, Deodhar, Turner, Caplan.

Acquisition of data. Ward, Deodhar, Shah, Sullivan, Turgunbaev, Oristaglio, Caplan.

Analysis and interpretation of data. Ward, Deodhar, Gensler, Dubreuil, Yu, Khan, Haroon, Borenstein, Wang, Biehl, Fang, Louie, Majithia, Ng, Bigham, Pianin, Shah, Sullivan, Turgunbaev, Oristaglio, Maksymowych, Caplan.

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RHEUMATOLOGY

Guidelines

Rheumatology 2017;56:313–316
doi:10.1093/rheumatology/kew223
Advance Access publication 24 August 2016

BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics

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Key words: ankylosing spondylitis, axial spondyloarthritis, anti-TNF, biologic, guideline, treatment

Executive Summary

Scope and purpose

Axial SpA (axSpA) is a chronic inflammatory condition predominantly involving the spine and sacroiliac joints (SIJ), with or without extra-spinal manifestations including peripheral arthritis, enthesitis, iritis, psoriasis and IBD. Individuals with axSpA experience significant pain, stiffness and lack of function that translates into important health care costs and increased mortality.

AxSpA can be classified into two subgroups: radiographic axSpA, commonly referred to as AS, and non-radiographic axSpA (nr-axSpA). The primary difference between these two subgroups is the presence or absence of defined structural changes in the SIJ as detected on plain radiography. Although patients with nr-axSpA do not fulfil the modified New York criteria for AS [1], their burden of disease is similar [2] and they may derive as much benefit from treatment as patients with established AS.

This revision of the 2005 BSR guidelines [3] provides evidence-based guidance for UK clinicians prescribing biologic drugs for adult patients across the spectrum of axSpA. This includes the criteria for starting treatment, the

NICE has accredited the process used by the BSR to produce its treatment of axial spondyloarthritis with biologics guidance. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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Submitted 8 October 2015; revised version accepted 12 April 2016

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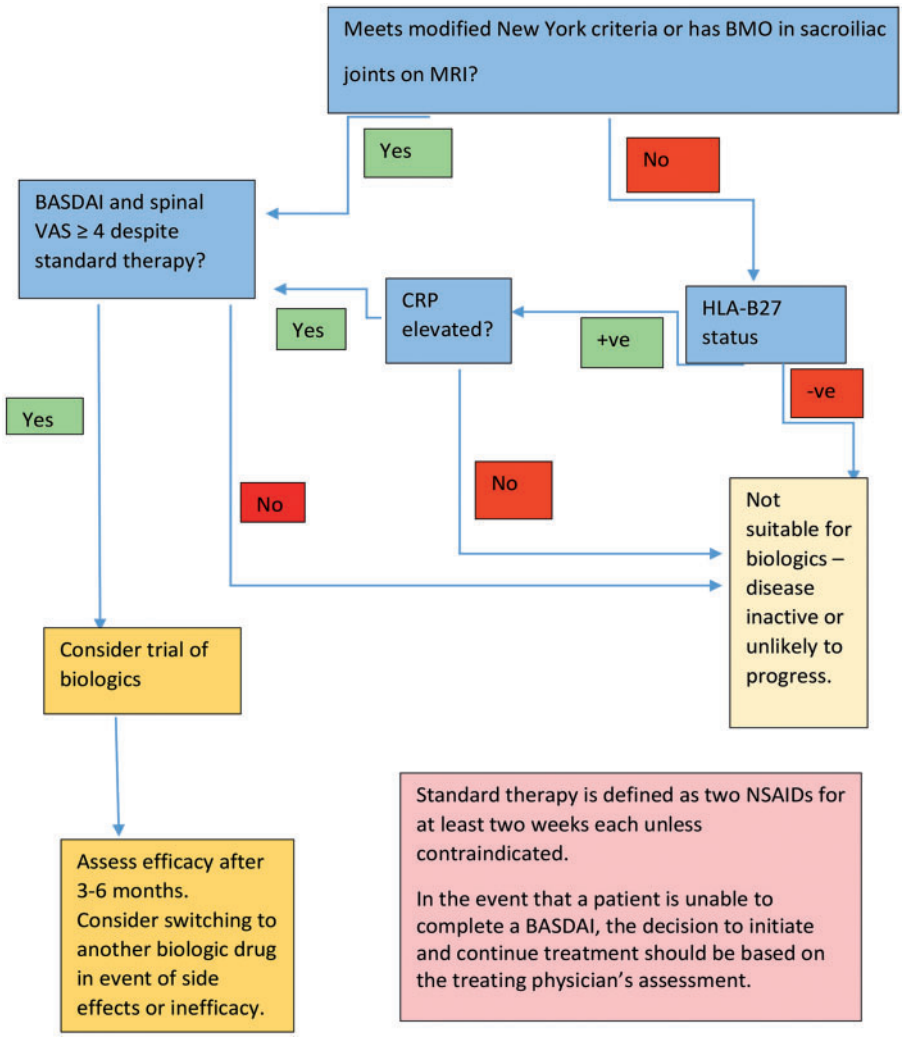
FIG. 1 Treatment algorithm for biologic therapy in axSpA


Meets modified New York criteria or has BMO in sacroiliac joints on MRI?
Yes
No
BASDAI and spinal VAS ≥ 4 despite standard therapy?
CRP elevated?
Yes
HLA-B27 status
+ve
-ve
Yes
No
No
Not suitable for biologics – disease inactive or unlikely to progress.
Consider trial of biologics
Assess efficacy after 3-6 months. Consider switching to another biologic drug in event of side effects or inefficacy.
Standard therapy is defined as two NSAIDs for at least two weeks each unless contraindicated.
In the event that a patient is unable to complete a BASDAI, the decision to initiate and continue treatment should be based on the treating physician's assessment.

BMO: bone marrow oedema; VAS: visual analogue scale.

choice of drug and assessing response to treatment. Peripheral spondyloarthritis and juvenile SpA are outside the scope of these guidelines, and readers are referred to the BSR 2012 guidelines for the management of PsA [4].

Key recommendations

These recommendations are summarized in a treatment algorithm (Fig. 1). Accompanying descriptions of evidence and full recommendations are given in the full guideline, provided as supplementary data, available at *Rheumatology* Online.

The effectiveness of biologics in axSpA

(i) Anti-TNF therapy is effective at reducing disease activity and spinal pain in axSpA. While short-term MRI data support the efficacy of anti-TNF therapy in treating inflammatory SIJ and spinal lesions in axSpA, evidence for anti-TNF therapy on radiographic disease progression is currently limited [level of evidence (LOE) 1+; strength of recommendation A; consensus score 9.6].

(ii) Currently there is insufficient evidence to recommend the use of other biologic agents in axSpA (LOE 1+; strength of recommendation B; consensus score 9.3).

Initiating treatment

(i) Patients should be considered for anti-TNF therapy if they have active axSpA (LOE 1+; strength of recommendation B; consensus score 9.6).

(ii) Active disease is defined as a BASDAI and spinal pain visual analogue scale (VAS) score $\geqslant 4$ despite standard therapy (LOE 1+; strength of recommendation B; consensus score 8.5).

(iii) The BASDAI should be measured on two occasions at least 4 weeks apart. Current National Institute for Health and Care Excellence guidelines require patients to have active spinal disease on two separate

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occasions 12 weeks apart, with the aim of avoiding the overtreatment of patients with a short-lived flare of disease. However, as flares in AS last for an average of 2–3 weeks [5], an interval of 4 weeks between scores is sufficient and should not delay treatment unduly (LOE 2+; strength of recommendation C; consensus score 7.2).

(iv) Patients with active disease who do not meet modified New York criteria for AS should also have had a positive MRI and/or raised CRP. Prescribers should be confident that worsening symptoms, radiological changes and raised inflammatory markers are due to axSpA and not to other pathology such as malignancy or infection. Discussion with an axSpA specialist should be considered before starting treatment in a patient with nr-axSpA and no SIJ bone marrow oedema on MRI (LOE 1+; strength of recommendation B; consensus score 9.3).

Choice of Drug

(i) Extra-articular manifestations and patient choice should be considered when selecting an anti-TNF agent. In the absence of head-to-head studies, systematic reviews have shown no statistical difference in efficacy between infliximab, golimumab, etanercept and adalimumab in the treatment of AS (certolizumab data were not included in these comparative reviews, but its efficacy has been established in clinical trials). There are insufficient data to comment on relative efficacy in nr-axSpA. However, not all biologics are licensed for or effective in the treatment of extra-articular disease, so drug choice should take into account co-morbidities and the preferred route and frequency of administration (LOE 4; strength of recommendation D; consensus score 8.9).

Assessing Response

(i) Initial efficacy response should be assessed following 3–6 months of therapy and responders should then be reassessed every 6 months (LOE 2+; strength of recommendation D; consensus score 8.6).

(ii) Response is defined as a reduction in the BASDAI and spinal pain VAS of $\geqslant 2$ U from baseline (LOE 1+; strength of recommendation B; consensus score 8.3).

(iii) If, because of cognitive or communication difficulties, the BASDAI cannot be used to monitor disease activity, the decision to initiate and continue therapy should be based on the treating clinician's assessment of disease activity (LOE 4; strength of recommendation D; consensus score 9.9).

Withdrawal of Therapy

(i) In the absence of an initial clinical response by 6 months, or failure to maintain response at two consecutive assessments, withdrawal of that anti-TNF agent should be considered (LOE 4; strength of recommendation D; consensus score 9.4).

(ii) There is no evidence to support the withdrawal of anti-TNF therapy in treatment responders (LOE 2+; strength of recommendation B; consensus score 9).

Switching

(i) In the event of anti-TNF failure due to inefficacy or adverse events, an alternative anti-TNF agent should be offered if clinically appropriate (LOE 2+; strength of recommendation C; consensus score 9.7).

Safety

The safety of anti-TNF therapies in axSpA is comparable to other inflammatory joint diseases such as RA. There is little evidence to suggest that safety issues differ hugely with different disease groups, and the 2010 British Society for Rheumatology (BSR) guidelines on the safety of anti-TNF therapies in RA are applicable in axSpA [6].

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this summary.

Disclosure statement: L.H. has received unit funding from AbbVie, MSD, Pfizer and UCB, was sponsored to attend a meeting by MSD and has received a research grant from Pfizer. G.J. has received unit funding from Pfizer and AbbVie and an honorarium from AbbVie. D.Mu. was sponsored to attend a meeting by MSD, has received honoraria from UCB and AbbVie and sits on an advisory board for AbbVie. R.S. is in receipt of research grants from Pfizer and AbbVie, has been sponsored to attend educational meetings by AbbVie and Novartis and has received honoraria from AbbVie, Novartis, Pfizer, UCB and MSD. N.B. has received unit funding from Novartis, was sponsored to attend a meeting by AbbVie and has received speaker fees from Pfizer and UCB. K.G. has received research grants and speaker fees from AbbVie, Pfizer, MSD, UCB and Novartis. S.S. has received research unit funding from Pfizer and Janssen; speaker fees from AbbVie, Pfizer, Amgen, UCB, Janssen, Novartis and MSD; honoraria or consultancies from BMS, MSD, AbbVie, UCB, Roche, Pfizer, Janssen, Boehringer Ingelheim and Novartis and has been sponsored to attend meetings by AbbVie, Janssen, UCB and MSD. K.R.M. is the lead organiser of the Rheumatology Education Symposium for General Practitioners, run by the Peninsula Rheumatologists, which has received a yearly educational grant of £4500 from AbbVie for the last 6 years and the Torbay Rheumatology Department has received a grant from AbbVie for a Mindfulness project. H.M.-O. has received honoraria from and acted as a consultant for AbbVie, Celgene, Novartis, UCB, Janssen and Pfizer and has received study grants from Janssen and Pfizer. D.Ma.

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has received honoraria from MSD, Pfizer, Wyeth, UCB and Celgene. L.v.R. has received honoraria and research support from Pfizer and AbbVie. The other authors have declared no conflicts of interest.

Supplementary data

The full guideline is available at *Rheumatology* Online and an audit tool to assess compliance with these recommendations can be found on the BSR website.

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Arthritis & Rheumatology
Vol. 71, No. 1, January 2019, pp 5–32
DOI 10.1002/art.40726
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SPECIAL ARTICLE

2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the health care provider in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

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Objective. To develop an evidence-based guideline for the pharmacologic and nonpharmacologic treatment of psoriatic arthritis (PsA), as a collaboration between the American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF).

Methods. We identified critical outcomes in PsA and clinically relevant PICO (population/intervention/comparator/outcomes) questions. A Literature Review Team performed a systematic literature review to summarize evidence supporting the benefits and harms of available pharmacologic and nonpharmacologic therapies for PsA. GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was used to rate the quality of the evidence. A voting panel, including rheumatologists, dermatologists, other health professionals, and patients, achieved consensus on the direction and the strength of the recommendations.

Results. The guideline covers the management of active PsA in patients who are treatment-naive and those who continue to have active PsA despite treatment, and addresses the use of oral small molecules, tumor necrosis factor inhibitors, interleukin-12/23 inhibitors (IL-12/23i), IL-17 inhibitors, CTLA4-Ig (abatacept), and a JAK inhibitor (tofacitinib). We also developed recommendations for psoriatic spondylitis, predominant enthesitis, and treatment in the presence of concomitant inflammatory bowel disease, diabetes, or serious infections. We formulated recommendations for a treat-to-target strategy, vaccinations, and nonpharmacologic therapies. Six percent of the recommendations were strong and 94% conditional, indicating the importance of active discussion between the health care provider and the patient to choose the optimal treatment.

Conclusion. The 2018 ACR/NPF PsA guideline serves as a tool for health care providers and patients in the selection of appropriate therapy in common clinical scenarios. Best treatment decisions consider each individual patient situation. The guideline is not meant to be proscriptive and should not be used to limit treatment options for patients with PsA.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, manifesting most commonly with peripheral arthritis, dactylitis, enthesitis, and spondylitis. Nail lesions, including pitting and onycholysis, occur in ~80–90% of patients with PsA. The incidence of PsA is ~6 per 100,000 per year, and the prevalence is ~1–2 per 1,000 in the general population (1). The annual incidence of PsA in patients with psoriasis is 2.7% (2), and the reported prevalence of PsA among patients with psoriasis has varied between 6% and 41% (1). In the majority of patients the skin symptoms develop first, followed by the arthritis; however, in some patients the skin and joint symptoms present at the same time, and in 10–15% the arthritis presents first (2).

PsA affects men and women equally. The distribution of the peripheral arthritis varies from asymmetric oligoarthritis (involving ≤4 joints) to symmetric polyarthritis (involving ≥5 joints). Distal interphalangeal joints are commonly affected and, in some patients, are the only affected joints. Axial disease, when present, usually occurs together with peripheral arthritis. Some patients present with rapidly progressive and destructive PsA–arthritis mutilans. PsA is associated with an adverse impact on health-related quality of life (3–5) and high health care costs and utilization (6,7). Greater disease activity is associated with progressive joint damage and higher mortality (8–11). Early identification of PsA and early initiation of therapy are important for improving long-term outcomes (12).

Both nonpharmacologic and pharmacologic treatment can ameliorate PsA symptoms and can occasionally result

This article is published simultaneously in *Arthritis Care & Research* and the *Journal of Psoriasis and Psoriatic Arthritis*.

Supported by the American College of Rheumatology and the National Psoriasis Foundation.

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Submitted for publication December 12, 2017; accepted in revised form September 11, 2018.

in disease remission (Figure 1). Clinicians and patients can now choose from a wide variety of pharmacologic therapies, including symptomatic treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs) and intraarticular injections, as well as immunomodulatory therapies.

The presentation of PsA is heterogeneous, and health care providers frequently face challenges when considering the various treatment options. Our objective was to develop evidence-based treatment recommendations for the management of active PsA in adults, using pharmacologic and nonpharmacologic therapies. These PsA treatment recommendations can help guide both clinicians and patients to arrive at optimal management decisions.

METHODS

Methodology overview. This guideline followed the American College of Rheumatology (ACR) guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process includes using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (13–15) (www.gradeworkinggroup.org) to rate the quality of the available evidence and to develop the recommendations. ACR policy guided disclosures and the management of conflicts of interest. The full methods are presented in detail in Supplementary Appendix 1, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract.

This work involved 4 teams selected by the ACR Quality of Care Committee after reviewing individual and group volunteer applications in response to an open request for proposals announcement: 1) a Core Leadership Team, which supervised and coordinated the project and drafted the clinical questions and manuscript; 2) a Literature Review Team, which completed the literature search and abstraction; 3) an Expert Panel, composed of patients, patient advocates, rheumatologists, dermatologists, 1 dermatologist-rheumatologist, and 1 rheumatology nurse practitioner, which developed the clinical questions (PICO [population/intervention/comparator/outcomes] questions) and decided on the scope of the guideline project; and 4) a Voting Panel, which included rheumatologists, 1 dermatologist, 1 dermatologist-rheumatologist, 1 rheumatology physician assistant, and 2 patients (1 of whom was also a physical therapist), who provided input from the patient perspective and voted on the recommendations. Additionally, a Patient Panel consisting of 9 adults with PsA reviewed the evidence and provided input on their values and preferences, which was reviewed before discussion of each section of PsA management (e.g., treatment-naive, treated, comorbidities), and was incorporated into discussions and formulation of recommendations. Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract) presents rosters of the team and panel members. In accordance with ACR policy, the principal investigator and the leader of the literature review team were free of conflicts, and within each team, >50% of the members were free of conflicts.

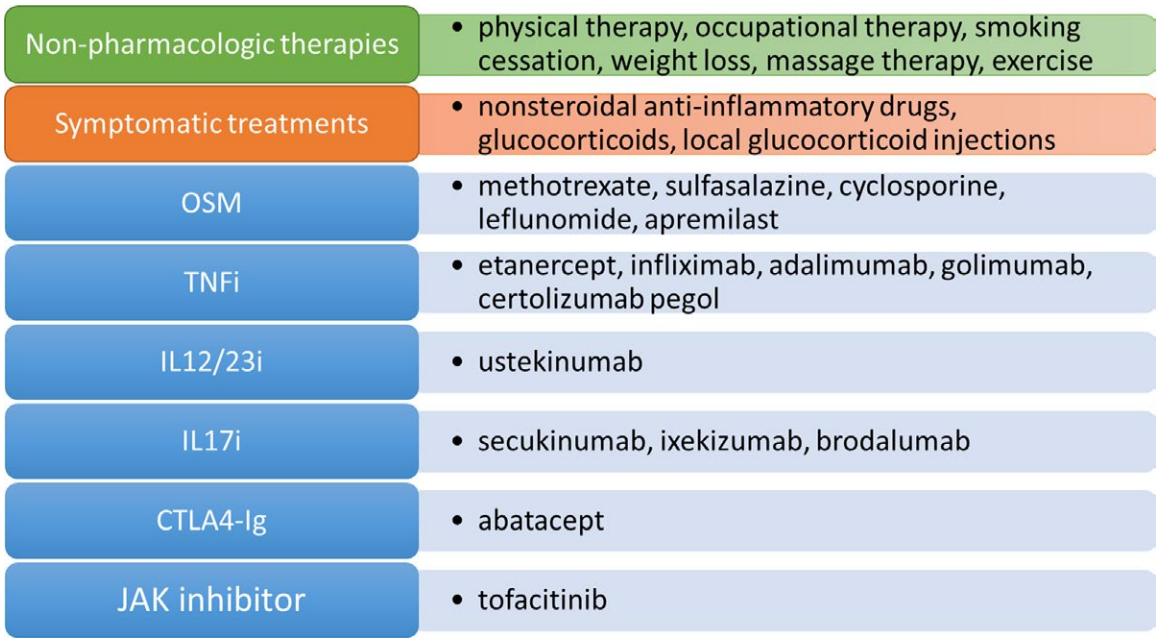

Figure 1. Pharmacologic, nonpharmacologic, and symptomatic therapies for psoriatic arthritis. Pharmacologic therapies are displayed in the blue boxes and include oral small molecules (OSMs), tumor necrosis factor inhibitor (TNFi) biologics, interleukin-17 inhibitor (IL-17i) biologics, an IL-12/23i biologic, CTLA4-immunoglobulin, and a JAK inhibitor. While there are numerous nonpharmacologic therapies available, 6 of these are addressed in this guideline. Symptomatic therapies include nonsteroidal antiinflammatory drugs, systemic glucocorticoids, and local glucocorticoid injections. Systemic glucocorticoids or local injections are not addressed in this guideline.

Framework for the PsA guideline development and scope of the guideline. Because there are numerous topics within PsA that could be addressed, at the beginning of the process the guideline panels made several decisions regarding the focus of this guideline and how to define aspects of the disease (e.g., active disease). At an initial scoping meeting, the Voting Panel and Expert Panel agreed that the project would include the management of patients with *active* PsA, defined as symptoms at an unacceptably bothersome level as reported by the patient and judged by the examining health care provider to be due to PsA based on the presence of at least 1 of the following: actively inflamed joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and/or extraarticular manifestations such as uveitis or inflammatory bowel disease (IBD). The health care provider may, in deciding if symptoms are due to active PsA, consider information beyond the core information from the history and physical examination, such as inflammation markers (C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]) and imaging results. At the scoping meeting, the panels decided that the guideline would address both pharmacologic and nonpharmacologic therapies for the treatment of PsA. We examined evidence regarding vaccinations, treatment in the presence of common comorbidities, and implementing a treat-to-target strategy.

In addressing pharmacologic therapies, we focused on immunomodulatory agents for long-term management rather than addressing acute symptom management (i.e., through intraarticular injections and the use of systemic glucocorticoids). Tofacitinib and ixekizumab were submitted for review and potential approval by the US Food and Drug Administration (FDA) at the time of formulation of this guideline (16,17) and for this reason, these drugs were addressed in the guideline. Both drugs have been approved for PsA since then (18,19). Tofacitinib is not included within the oral small molecules (OSM) category since its benefit/risk profile differs from that of the rest of the OSMs, especially with regard to risks (20–22), and consistent with its being considered separately in other treatment guidelines (23,24). Additionally, the panel addressed alternatives in patient subpopulations (e.g., patients with predominant enthesitis, axial disease, dactylitis, comorbidities), and greater versus lesser disease severity.

There are currently no widely agreed-upon definitions of disease severity in PsA or psoriasis. Thus, health care providers and patients should judge PsA and psoriasis severity on a case-by-case basis. For the purpose of these recommendations, severity includes not only the level of disease activity at a given time point, but also the presence or absence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of 1 or more of the following: a poor prognostic factor (erosive disease, dactylitis, elevated levels of inflammation markers such as ESR and CRP attributable to PsA), long-term damage that interferes with function (e.g., joint deformities), highly active disease that causes a major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease (Figure 2). In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) (25) score of ≥12 and a body surface area score of ≥10. However, because it is cumbersome, physicians seldom use the PASI in clinical practice. Examples of definitions of severe PsA and severe psoriasis are shown in Figure 2. Finally, because the National Psoriasis Foundation (NPF) and American Academy of Dermatology are concurrently developing psoriasis treatment guidelines, the treatment of skin psoriasis separately from the inflammatory arthritis was not included in the current ACR/NPF PsA guideline.

Systematic synthesis of the literature. Systematic searches of the published English-language literature included Ovid Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from the beginning of each database through November 15, 2016 (Supplementary Appendix 3, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract); we conducted updated searches on May 2, 2017 and again on March 8, 2018. DistillerSR software (https://distillercer.com/products/distillersr-systematic-reviewsoftware/) (Supplementary Appendix 4; http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract) was used to facilitate duplicate screening of literature search results. Reviewers entered extracted data into RevMan software (http://tech.cochrane.org/revman), and evaluated the risk of bias in primary studies using the Cochrane risk of bias tool (http://handbook.cochrane.org/). We exported RevMan files into GRADEpro software to formulate a GRADE summary of findings table (Supplementary Appendix 5; http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract) for each PICO question (26). Additionally, a network meta-analysis was performed when sufficient studies were available. GRADE criteria provided the framework for judging the overall quality of evidence (13).

The panels chose the critical outcomes for all comparisons at the initial scoping; these included the American College of Rheumatology 20% response criteria (ACR20) (the primary outcome for most PsA clinical trials), the Health Assessment Questionnaire disability index (a measure of physical function), the PASI 75% response criteria (PASI75) (a measure of skin psoriasis improvement), and serious infections. Both the ACR20 and the PASI75 are accepted outcome measures specified by regulatory agencies, including the US FDA, for the approval of treatments for PsA (27). Serious infections are among the issues of greatest

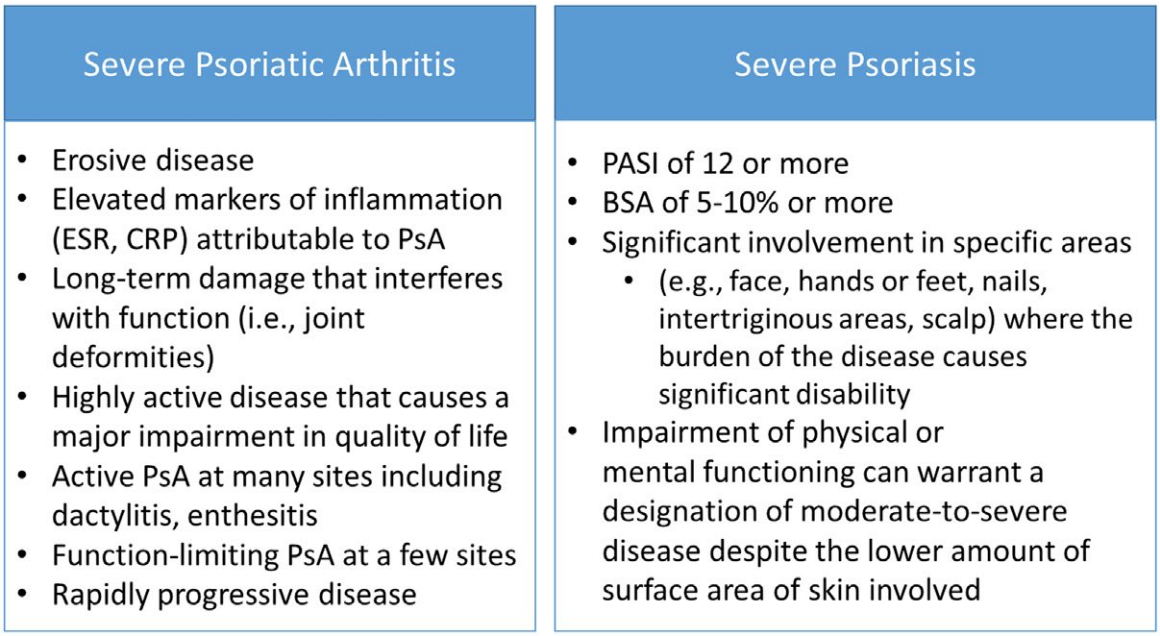
Severe Psoriatic Arthritis
• Erosive disease
• Elevated markers of inflammation (ESR, CRP) attributable to PsA
• Long-term damage that interferes with function (i.e., joint deformities)
• Highly active disease that causes a major impairment in quality of life
• Active PsA at many sites including dactylitis, enthesitis
• Function-limiting PsA at a few sites
• Rapidly progressive disease
Severe Psoriasis
• PASI of 12 or more
• BSA of 5-10% or more
• Significant involvement in specific areas
• (e.g., face, hands or feet, nails, intertriginous areas, scalp) where the burden of the disease causes significant disability
• Impairment of physical or mental functioning can warrant a designation of moderate-to-severe disease despite the lower amount of surface area of skin involved

Figure 2. Examples of "severe" psoriatic arthritis (PsA) and psoriasis. The guideline development group defined severe PsA and psoriasis as the presence of 1 or more of the items listed. This is not a formal definition. There have been many definitions of severe psoriasis used over time—the items here are adapted from the 2007 National Psoriasis Foundation expert consensus statement for moderate-to-severe psoriasis (68). In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score of ≥12 and a body surface area (BSA) score of ≥10 (25). ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

concern for patients and physicians when selecting among therapies. Other specific harms (e.g., liver toxicity with methotrexate [MTX]) were included as critical outcomes for individual comparisons. We included other outcomes, such as total infections (regardless of severity), when appropriate.

Moving from evidence to recommendations. GRADE methodology specifies that panels make recommendations based on the balance of benefits and harms, the quality of the evidence (i.e., confidence in effect estimates), and patients' values and preferences. Deciding on the balance between desirable and undesirable outcomes requires estimating the relative value patients place on those outcomes. When the literature provided very limited guidance, the experience of the Voting Panel members (including physicians, a rheumatology physician assistant, and the 2 patients present) in managing the relevant cases and issues became an important source of evidence. Values and preferences, crucial to all recommendations, derived from input from the members of the Patient Panel were particularly salient in such situations. GRADE methodology allows the panels the possibility of not coming to a decision, and a summary of the discussion is noted in such cases. However, during the development of this guideline, the Voting Panel came to a conclusion in each case scenario, and such a situation did not arise.

Consensus building. The Voting Panel voted on the direction and strength of the recommendation related to each PICO question. Recommendations required a 70% level of agreement, as used previously in other similar processes (28) and in the previous ACR guidelines (23,29,30); if 70% agreement was not achieved during an initial vote, the panel members held additional discussions before revoting. For all conditional recommendations, a written explanation is provided, describing the reasons for the decision and conditions under which the alternative choice may be preferable.

Moving from recommendations to practice. These recommendations are designed to help health care providers work with patients in selecting therapies. The presence or absence of concomitantly occurring conditions, such as IBD, uveitis, diabetes, and serious infections, and the knowledge of previous therapies, influence decisions regarding optimal management. In the context of PsA, the physical examination, which is also required for selecting therapy, includes assessment of the peripheral joints (including for dactylitis), the entheses, the spine, the skin, and the nails. Health care providers and patients must take into consideration all active disease domains, comorbidities, and the patient's functional status in choosing the optimal therapy for an individual at a given point in time.

RESULTS/RECOMMENDATIONS

How to interpret the recommendations

1. A *strong recommendation* means that the panel was *confident* that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion of clinicians/patients not wanting to follow the recommendation. We use the phrase "*should use*" or "*should be used*" for strong recommendations.
2. A *conditional recommendation* means that the panel believed the desirable effects of following the recommendation *probably* outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but a small proportion of clinicians/patients may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. We use the phrase "*is recommended over*" or "*is/would be recommended*" for conditional recommendations. We specify conditions under which the less preferred drug may be used by using the phrase "*may be used*" or "*may consider*" or "*Y (less preferred drug) may be used instead of X (preferred drug)*" or "*may consider Y instead of X (preferred drug)*" for conditional recommendations.
3. Conditional recommendations were usually based on low- to very-low-quality evidence (in rare instances, moderate-quality evidence). Strong recommendations were typically based on moderate- or high-quality evidence.
4. For each recommendation, Supplementary Appendix 5 (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract) provides details regarding the PICO questions and the GRADE evidence tables.
5. In each case, the Voting Panel's recommendation was based on a judgment of the most likely net benefit, i.e.,1) more benefit with the medication conditionally recommended with no difference in harms between the medications being compared (e.g., choosing a TNFi over OSMs in treatment-naive patients) or 2) less harm with the medication conditionally recommended and no difference in benefit (e.g., choosing abatacept over a TNFi in patients at risk of or with a history of previous infections, or preferring a different OSM over MTX in patients with PsA and diabetes due to an increased risk of liver toxicity in this subpopulation).
6. This is an evidence-based guideline, in that we explicitly use the best evidence available and present that in a transparent manner for the clinician reader/user (31,32). In some instances, this includes a randomized trial directly comparing the interventions under consideration. In other cases, in the absence of any published evidence, the best evidence comes from the collective experience of the Voting Panel and patient panel members, which in the GRADE system is rated as "very-low-quality" evidence.

Recommendations for pharmacologic interventions

Active PsA in treatment-naive patients (Table 1 and Figure 3). *All recommendations for treatment-naive patients with active PsA are conditional based on low- to very-low-quality evidence.*

In treatment-naive patients with active PsA, a TNFi biologic agent is recommended over an OSM as a first-line option (Table 1). OSMs may be used instead of a TNFi biologic in patients without severe PsA and without severe psoriasis (as defined in Methods and Figure 2; final determination of severity to be made by the patient and the health care provider), those who prefer an oral drug instead of parenteral therapy, or those with contraindications to TNFi treatment, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.

For treatment-naive patients with active PsA, the use of a TNFi biologic or OSM is recommended over an interleukin-17 inhibitor (IL-17i) or IL-12/23i biologic. An IL-17i or IL-12/23i biologic may be used instead of TNFi biologics in patients with severe psoriasis or contraindications to TNFi biologics, and may be used instead of OSMs in patients with severe psoriasis or severe PsA. MTX is recommended over NSAIDs in treatment-naive patients with active PsA. NSAIDs may be used instead of MTX after consideration of possible contraindications and side effect profile in patients without evidence of severe PsA or severe psoriasis and in those at risk for liver toxicity (Table 1 and Figure 3). An IL-17i biologic is recommended over an IL-12/23i biologic. IL-12/23i biologics may be used in patients who have concomitant IBD or who desire less frequent drug administration.

Active PsA despite treatment with an OSM (Table 2 and Figure 4). *All recommendations for patients with active PsA despite treatment with an OSM are conditional based on mostly low- to very-low-quality evidence and, in a few instances, moderate-quality evidence.*

In patients with active PsA despite OSM therapy, switching to a TNFi, an IL-17i, or an IL-12/23i biologic is recommended over switching to a different OSM (Table 2 and Figure 4). A different OSM may be used rather than a TNFi, IL-17i, or IL-12/23i in patients who prefer an oral medication or those without evidence of severe PsA or severe psoriasis; a differ-

Table 1. Recommendations for the initial treatment of patients with active psoriatic arthritis who are OSM- and other treatment–naive (PICOs 9–15)*

	Level of evidence (evidence [refs.] reviewed)†
In OSM- and other treatment–naive patients with active PsA,	
1. **Treat with a TNFi biologic over an OSM** (MTX, SSZ, LEF, CSA, or APR) (PICO 10a–e) **Conditional recommendation** based on low-quality evidence; may consider an OSM if the patient does not have severe PsA,‡ does not have severe psoriasis,§ prefers oral therapy, has concern over starting a biologic as the first therapy, or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (53–66)
2. **Treat with a TNFi biologic over an IL-17i biologic** (PICO 14) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i biologic if the patient has severe psoriasis or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
3. **Treat with a TNFi biologic over an IL-12/23i biologic** (PICO 13) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has severe psoriasis, prefers less frequent drug administration, or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
4. **Treat with an OSM over an IL-17i biologic** (PICO 12) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i biologic if the patient has severe psoriasis and/or severe PsA.	Very low
5. **Treat with an OSM over an IL-12/23i biologic** (PICO 11) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD and/or severe psoriasis and/or severe PsA or prefers less frequent drug administration.	Very low
6. **Treat with MTX over NSAIDs** (PICO 9) **Conditional recommendation** based on very-low-quality evidence; may consider NSAIDs before starting MTX in patients with less active disease, after careful consideration of cardiovascular risks and renal risks of NSAIDs.	Very low (67)
7. **Treat with an IL-17i biologic over an IL-12/23i biologic** (PICO 15) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD or prefers less frequent drug administration.	Very low

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), cyclosporine (CSA), or apremilast (APR) and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. OSM- and other treatment–naive is defined as naive to treatment with OSMs, tumor necrosis factor inhibitors (TNFi,) interleukin-17 inhibitors (IL-17i), and IL-12/23i; patients may have received nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, and/or other pharmacologic and nonpharmacologic interventions.

† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.

§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

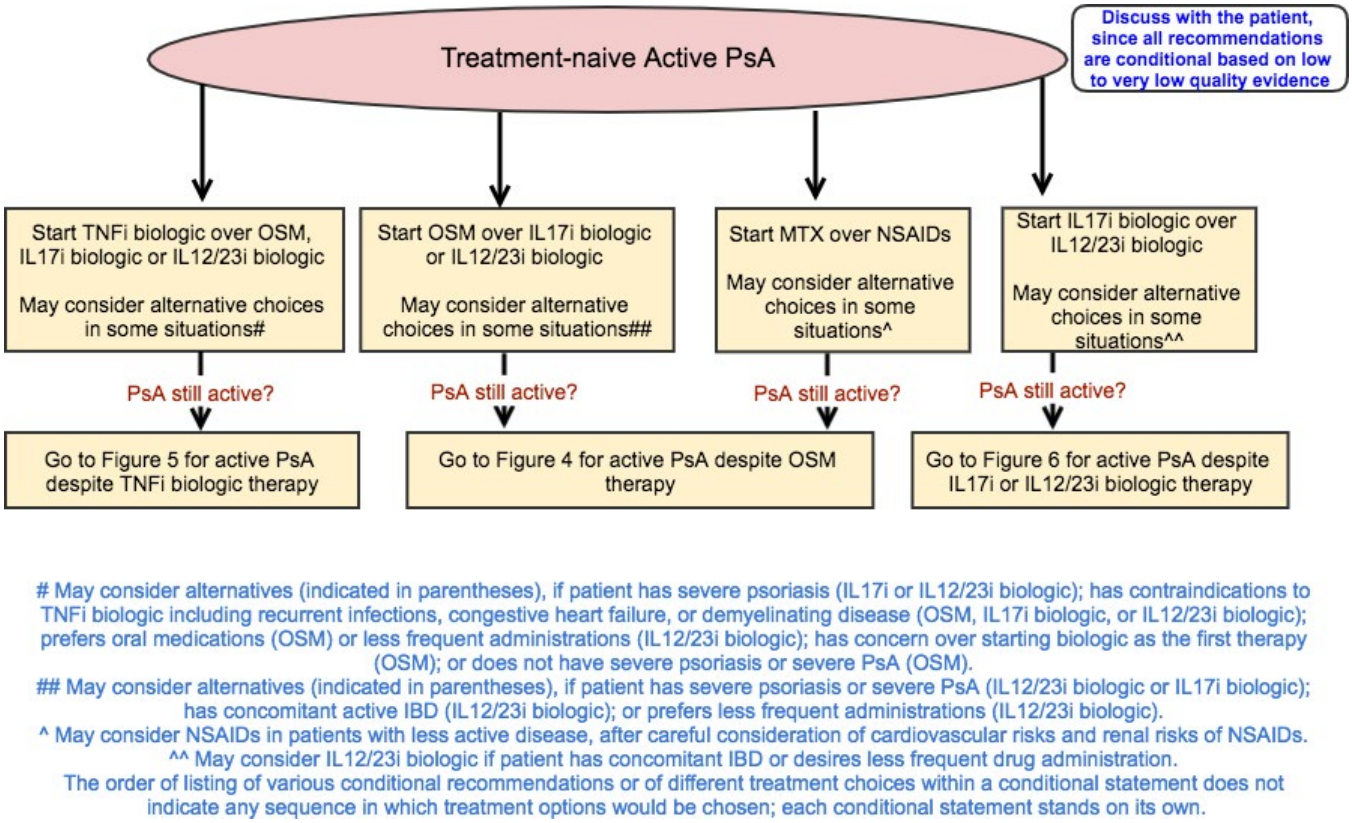
Treatment-naive Active PsA
Discuss with the patient, since all recommendations are conditional based on low to very low quality evidence
Start TNFi biologic over OSM, IL17i biologic or IL12/23i biologic
May consider alternative choices in some situations#
Start OSM over IL17i biologic or IL12/23i biologic
May consider alternative choices in some situations##
Start MTX over NSAIDs
May consider alternative choices in some situations^
Start IL17i biologic over IL12/23i biologic
May consider alternative choices in some situations^^
PsA still active?
PsA still active?
PsA still active?
PsA still active?
Go to Figure 5 for active PsA despite TNFi biologic therapy
Go to Figure 4 for active PsA despite OSM therapy
Go to Figure 6 for active PsA despite IL17i or IL12/23i biologic therapy
May consider alternatives (indicated in parentheses), if patient has severe psoriasis (IL17i or IL12/23i biologic); has contraindications to TNFi biologic including recurrent infections, congestive heart failure, or demyelinating disease (OSM, IL17i biologic, or IL12/23i biologic); prefers oral medications (OSM) or less frequent administrations (IL12/23i biologic); has concern over starting biologic as the first therapy (OSM); or does not have severe psoriasis or severe PsA (OSM).
May consider alternatives (indicated in parentheses), if patient has severe psoriasis or severe PsA (IL12/23i biologic or IL17i biologic); has concomitant active IBD (IL12/23i biologic); or prefers less frequent administrations (IL12/23i biologic).
^ May consider NSAIDs in patients with less active disease, after careful consideration of cardiovascular risks and renal risks of NSAIDs.
^^ May consider IL12/23i biologic if patient has concomitant IBD or desires less frequent drug administration.
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

Figure 3. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) who are treatment-naive (no exposure to oral small molecules [OSMs] or other treatments). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 1 and the related section in the Results. This figure is derived from recommendations based on PICO (population/intervention/comparator/outcomes) questions that are based on the common clinical situations. Active PsA was defined as symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining health care provider to be due to PsA based on the presence of at least 1 of the following: actively inflamed joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and/or extraarticular manifestations such as uveitis or inflammatory bowel disease (IBD). TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor; MTX = methotrexate; NSAIDs = nonsteroidal antiinflammatory drugs.

ent OSM may be used rather than a TNFi in the presence of contraindications to TNFi biologics. A TNFi biologic is recommended over an IL-17i biologic, an IL-12/23i biologic, abatacept, or tofacitinib. An IL-17i biologic is recommended over an IL-12/23i biologic, abatacept, or tofacitinib. An IL-12/23i is recommended over abatacept or tofacitinib. In patients with contraindications to TNFi agents, an IL-12/23i, an IL-17i, abatacept, or tofacitinib may be used instead of a TNFi. In patients with severe psoriasis, an IL-12/23i or an IL-17i may be used instead of a TNFi. Tofacitinib may be used instead of a TNFi in patients preferring oral medication who do not have severe psoriasis.

Switching to another OSM is recommended over adding another OSM to the current treatment (except in the case of apremilast). Adding another OSM (except apremilast) to current treatment may be considered if the patient has exhibited partial response to the current OSM. Adding apremilast to the current OSM therapy is recommended over switching to apremilast monotherapy since most evidence for benefits of apremilast pertains to apremilast combination therapy. Switching to apremilast monotherapy may be considered instead of apremilast combination therapy if the patient has intolerable side effects with the current OSM.

Biologic monotherapy is recommended over biologic combination therapy with MTX (the most commonly used OSM in combination therapy). When switching to biologic monotherapy, stopping the OSM or tapering of the OSM are both reasonable options and depend on patient and health care provider

Table 2. Recommendations for treatment of patients with active psoriatic arthritis despite treatment with an OSM (PICOs 16–25; 67–69; 76–78)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA despite treatment with an OSM,	
1. **Switch to a TNFi biologic over a different OSM** (PICO 23) **Conditional recommendation** based on moderate-quality evidence; may consider switching to a different OSM if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, if the patient prefers an oral versus parenteral therapy, or in patients without evidence of severe PsA‡ or severe psoriasis.§	Moderate (62–66, 69–86)
2. **Switch to a TNFi biologic over an IL-17i biologic** (PICO 17) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-17i if the patient has severe psoriasis and/or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, and/or a family history of demyelinating disease such as multiple sclerosis.	Moderate (62–66, 72–78, 87–97)
3. **Switch to a TNFi biologic over an IL-12/23i biologic** (PICO 16) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-12/23i if the patient has severe psoriasis and/or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.	Moderate (62–66, 72–78, 97–102)
4. **Switch to a TNFi biologic over abatacept** (PICO 67) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (62–66, 72–78, 103, 104)
5. **Switch to a TNFi biologic over tofacitinib** (PICO 76) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers oral medication.	Low (62–66, 72–78, 105)
6. **Switch to an IL-17i over a different OSM** (PICO 25) **Conditional recommendation** based on low-quality evidence; may consider switching to a different OSM if the patient prefers an oral versus parenteral therapy or in patients without evidence of severe PsA or severe psoriasis.	Low (79–87, 89–95)
7. **Switch to an IL-17i biologic over an IL-12/23i biologic** (PICO 18) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD or prefers less frequent drug administration.	Moderate (87, 89–95, 98–100, 106, 107)
8. **Switch to an IL-17i biologic over abatacept** (PICO 69) **Conditional recommendation** based on low-quality evidence; may consider abatacept in patients with recurrent or serious infections.	Low (89–95, 103, 104)
9. **Switch to an IL-17i biologic over tofacitinib** (PICO 78) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or has a history of recurrent *Candida i*nfections.	Low (89–95, 105)
10. **Switch to an IL-12/23i biologic over a different OSM** (PICO 24) **Conditional recommendation** based on low-quality evidence; may consider switching to a different OSM if the patient prefers an oral versus parenteral therapy or in patients without evidence of severe PsA or severe psoriasis.	Low (79–86, 98–100)
11. **Switch to an IL-12/23i biologic over abatacept** (PICO 68) **Conditional recommendation** based on low-quality evidence; may consider abatacept in patients with recurrent or serious infections.	Low (98–100, 103, 104)

Table 2. *(Cont'd)*

	Level of evidence (evidence [refs.] reviewed)†
12. **Switch to an IL-12/23i biologic over tofacitinib** (PICO 77) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy.	Low (98–100, 105)
13. **Add apremilast to current OSM therapy over switching to apremilast** (PICO 22b) **Conditional recommendation** based on low-quality evidence; may consider switching to apremilast if the patient has intolerable side effects with the current OSM.	Low (83, 84, 108)
14. **Switch to another OSM (except apremilast) over adding another OSM (except apremilast) to current treatment** (PICO 22a) **Conditional recommendation** based on low-quality evidence; may consider adding another OSM (except apremilast) to current treatment if the patient has demonstrated partial response to the current OSM.	Low (83, 84, 108)
15. **Switch to a TNFi biologic monotherapy over MTX and a TNFi biologic combination therapy** (PICO 19) **Conditional recommendation** based on low-quality evidence; may consider MTX and TNFi biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, has concomitant uveitis (since uveitis may respond to MTX therapy), and if the current TNFi biologic is infliximab or adalimumab.	Low (109–111)
16. **Switch to an IL-17i biologic monotherapy over MTX and an IL-17i biologic combination therapy** (PICO 21) **Conditional recommendation** based on very-low-quality evidence; may consider MTX and an IL-17i biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy).	Very low
17. **Switch to an IL-12/23i biologic monotherapy over MTX and an IL-12/23i biologic combination therapy** (PICO 20) **Conditional recommendation** based on very-low-quality evidence; may consider MTX and an IL-12/23i biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy).	Very low

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine, or apremilast and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor.

† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.

§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

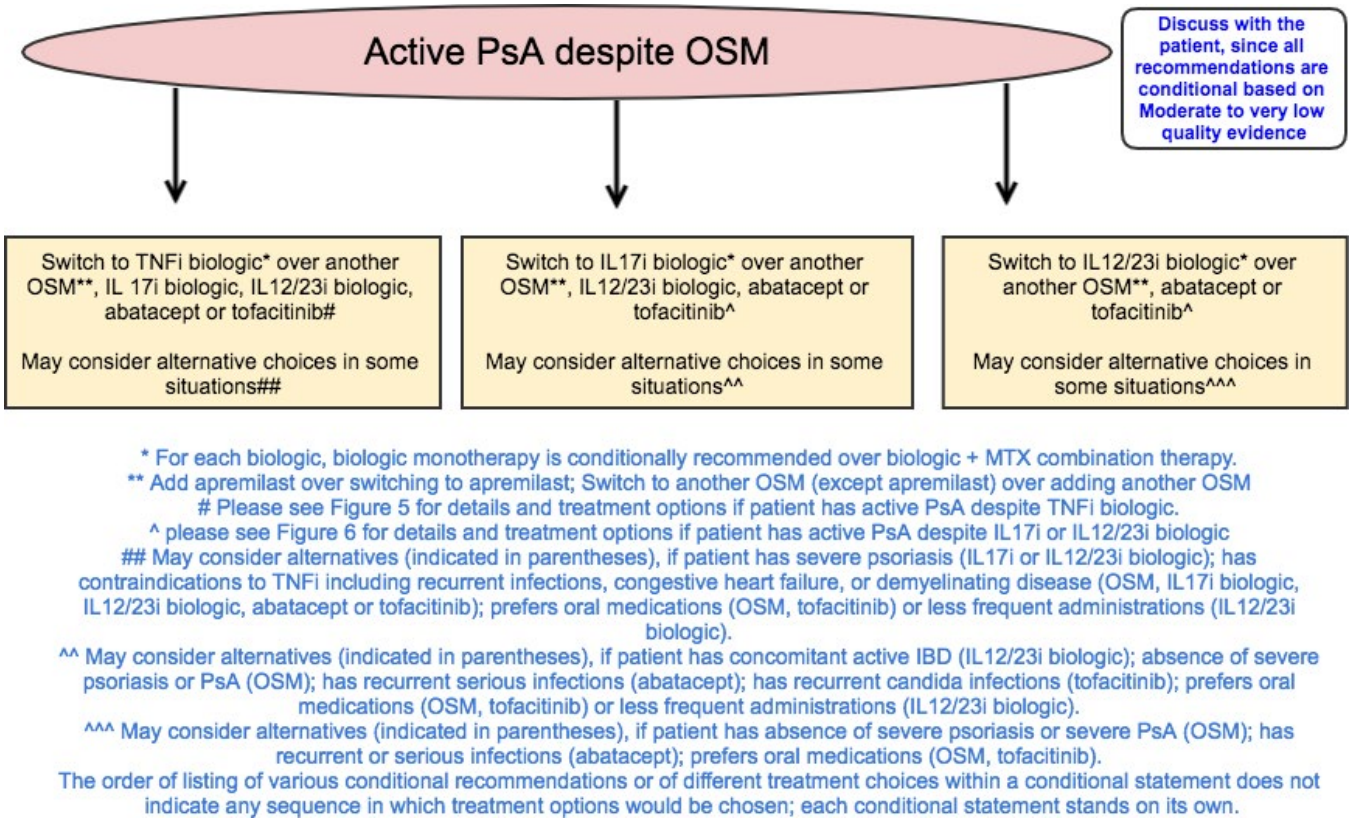
Active PsA despite OSM
Discuss with the patient, since all recommendations are conditional based on Moderate to very low quality evidence
Switch to TNFi biologic* over another OSM**, IL 17i biologic, IL12/23i biologic, abatacept or tofacitinib#
May consider alternative choices in some situations##
Switch to IL17i biologic* over another OSM**, IL12/23i biologic, abatacept or tofacitinib^
May consider alternative choices in some situations^^
Switch to IL12/23i biologic* over another OSM**, abatacept or tofacitinib^
May consider alternative choices in some situations^^^
* For each biologic, biologic monotherapy is conditionally recommended over biologic + MTX combination therapy.
** Add apremilast over switching to apremilast; Switch to another OSM (except apremilast) over adding another OSM
# Please see Figure 5 for details and treatment options if patient has active PsA despite TNFi biologic.
^ please see Figure 6 for details and treatment options if patient has active PsA despite IL17i or IL12/23i biologic
May consider alternatives (indicated in parentheses), if patient has severe psoriasis (IL17i or IL12/23i biologic); has contraindications to TNFi including recurrent infections, congestive heart failure, or demyelinating disease (OSM, IL17i biologic, IL12/23i biologic, abatacept or tofacitinib); prefers oral medications (OSM, tofacitinib) or less frequent administrations (IL12/23i biologic).
^^ May consider alternatives (indicated in parentheses), if patient has concomitant active IBD (IL12/23i biologic); absence of severe psoriasis or PsA (OSM); has recurrent serious infections (abatacept); has recurrent candida infections (tofacitinib); prefers oral medications (OSM, tofacitinib) or less frequent administrations (IL12/23i biologic).
^^^ May consider alternatives (indicated in parentheses), if patient has absence of severe psoriasis or severe PsA (OSM); has recurrent or serious infections (abatacept); prefers oral medications (OSM, tofacitinib).
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

Figure 4. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with oral small molecules (OSMs). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 2 and the related section in the Results. TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor; MTX = methotrexate.

preferences. A biologic agent in combination with MTX may be used instead of biologic monotherapy if the patient has severe psoriasis, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy), or in patients receiving treatment with a monoclonal antibody TNFi biologic, especially infliximab and adalimumab, to potentially delay or prevent the formation of antidrug antibodies.

Active PsA despite treatment with a TNFi biologic agent as monotherapy or in combination therapy (Table 3 and Figure 5). *All recommendations for patients with active PsA despite TNFi biologic treatment are conditional based on low- to very-low-quality evidence.*

In patients with active PsA despite treatment with TNFi biologic monotherapy, switching to a different TNFi biologic monotherapy is recommended over switching to IL-12/23i biologic, an IL-17i biologic, abatacept, or tofacitinib monotherapy or adding MTX to the current TNFi biologic (Table 3 and Figure 5). An IL-12/23i biologic, IL-17i biologic, abatacept, or tofacitinib may be used instead of a different TNFi biologic monotherapy in the case of a primary TNFi biologic failure or a serious adverse event due to the TNFi biologic. An IL-17i or IL-12/23i biologic may be used instead of a different TNFi biologic, particularly in the presence of severe psoriasis. Abatacept may be used instead of a TNFi biologic in patients with recurrent or serious infections in the absence of severe psoriasis, based on indirect evidence of fewer hospitalized infections with abatacept compared to TNFi biologics in a population with rheumatoid arthritis (33). Tofacitinib may be used instead of a TNFi biologic if oral therapy is preferred by the patient.

In patients with active PsA despite treatment with TNFi biologic monotherapy, an IL-17i biologic is recommended over an IL-12/23i biologic, abatacept, or tofacitinib, and an IL-12/23i biologic is recommended over abatacept or tofacitinib. An IL-12/23i biologic may be considered instead of an IL-17i biologic if the patient has IBD or desires less frequent drug administration. Abatacept may be considered instead of an IL-17i or IL-

Table 3. Recommendations for treatment of patients with active psoriatic arthritis despite treatment with a TNFi biologic, as monotherapy or in combination with MTX (PICOs 26–35; 70–75)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA despite treatment with a TNFi biologic monotherapy,	
1. **Switch to a different TNFi biologic over switching to an IL-17i biologic** (PICO 28) **Conditional recommendation** based on low-quality evidence; may consider an IL-17i if the patient had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse event or severe psoriasis.‡	Low (72, 73, 90–93, 95)
2. **Switch to a different TNFi biologic over switching to an IL-12/23i biologic** (PICO 27) **Conditional recommendation** based on low-quality evidence; may consider an IL-12/23i if the patient had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse effect or prefers less frequent drug administration.	Low (72, 73, 99, 100)
3. **Switch to a different TNFi biologic over switching to abatacept** (PICO 70) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient had a primary TNFi biologic efficacy failure or TNFi biologic–associated serious adverse effect.	Low (72, 73, 103, 104)
4. **Switch to a different TNFi biologic over switching to tofacitinib** (PICO 73) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse effect.	Low (62–66, 72–78, 105)
5. **Switch to a different TNFi biologic (with or without MTX) over adding MTX to the same TNFi biologic monotherapy** (PICO 26 and 26A) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX when patients have demonstrated partial response to the current TNFi biologic therapy, especially if the TNFi biologic is a monoclonal antibody.	Very low
6. **Switch to an IL-17i biologic over switching to an IL-12/23i biologic** (PICO 29) **Conditional recommendation** based on low-quality evidence; may consider an IL-12/23i if the patient has IBD or if the patient prefers less frequent drug administration.	Low (90–93, 95, 99, 100)
7. **Switch to an IL-17i biologic over abatacept** (PICO 72) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient prefers IV dosing or in patients with recurrent or serious infections.	Low (90–93, 95, 103, 104, 112)
8. **Switch to an IL-17i biologic over tofacitinib** (PICO 75) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or in patients with concomitant IBD or a history of recurrent *Candida* infections.	Low (90–93, 105)
9. **Switch to an IL-12/23i biologic over abatacept** (PICO 71) **Conditional recommendation** based on of low-quality evidence; may consider abatacept if the patient prefers IV dosing or in patients with recurrent or serious infections.	Low (99, 100, 103, 104)
10. **Switch to an IL-12/23i biologic over tofacitinib** (PICO 74) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy.	Low (98–100, 105)
11. **Switch to a different TNFi biologic monotherapy over switching to a different TNFi biologic and MTX combination therapy** (PICO 30) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a TNFi biologic and MTX combination therapy if the current TNFi biologic is infliximab.	Very low
12. **Switch to an IL-17i biologic monotherapy over switching to an IL-17i biologic and MTX combination therapy** (PICO 32) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-17i biologic and MTX combination therapy in patients with concomitant uveitis, as uveitis may respond to MTX therapy.	Very low

Table 3. *(Cont'd)*

	Level of evidence (evidence [refs.] reviewed)†
13. **Switch to an IL-12/23i biologic monotherapy over switching to an IL-12/23i biologic and MTX combination therapy** (PICO 31) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-12/23i biologic and MTX combination therapy if the patient has severe psoriasis.	Very low
In adult patients with active PsA despite treatment with a TNFi biologic and MTX combination therapy,	
14. **Switch to a different TNFi biologic + MTX over switching to a different TNFi biologic monotherapy** (PICO 33) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different TNFi biologic monotherapy if the patient has demonstrated MTX-associated adverse events, prefers to receive fewer medications, or perceives MTX as a burden.	Very low
15. **Switch to an IL-17i biologic monotherapy over an IL-17i biologic and MTX combination therapy** (PICO 35) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-17i biologic and MTX combination therapy if the patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL-17i biologic was discussed as potentially beneficial to allow the new therapy time to work.	Very low
16. **Switch to IL-12/23i biologic monotherapy over IL-12/23i biologic and MTX combination therapy** (PICO 34) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-12/23i biologic and MTX combination therapy if the patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL-12/23i biologic was discussed as potentially beneficial to allow the new therapy time to work.	Very low

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). TNFi = tumor necrosis factor inhibitor; MTX = methotrexate; IL-17i = interleukin-17 inhibitor; IV = intravenous.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

12/23i biologic in patients with recurrent or serious infections. Tofacitinib may be considered instead of an IL-17i biologic in patients who prefer oral therapy or have a history of recurrent or severe *Candida* infections. Tofacitinib may be considered instead of an IL-12/23i biologic in patients who prefer oral therapy. For each biologic (TNFi, IL-12/23i, or IL-17i), monotherapy is recommended over combination with MTX. Combination therapy with biologic and MTX may be used instead of biologic monotherapy in the presence of severe psoriasis, partial response to current MTX therapy, concomitant uveitis (since uveitis may respond to MTX therapy), and if the current TNFi biologic is infliximab or adalimumab (for immunogenicity prevention).

Under circumstances in which combination therapy with a TNFi biologic and MTX is used and active PsA persists, switching to a different TNFi with MTX is recommended over monotherapy with a different TNFi. Continuing MTX treatment during TNFi transition was seen as beneficial because TNFi biologics may have more sustained efficacy when used in combination with MTX, but evidence is limited (34). Monotherapy with a different TNFi biologic may be used if the patient has had MTX-associated adverse events, prefers to receive fewer medications, or perceives MTX treatment as a burden. IL-12/23i or IL-17i biologic monotherapy is recommended over either of these agents in combination with MTX. Combination therapy with an IL-17i or IL-12/23 biologic and MTX may be used instead of switching to biologic monotherapy

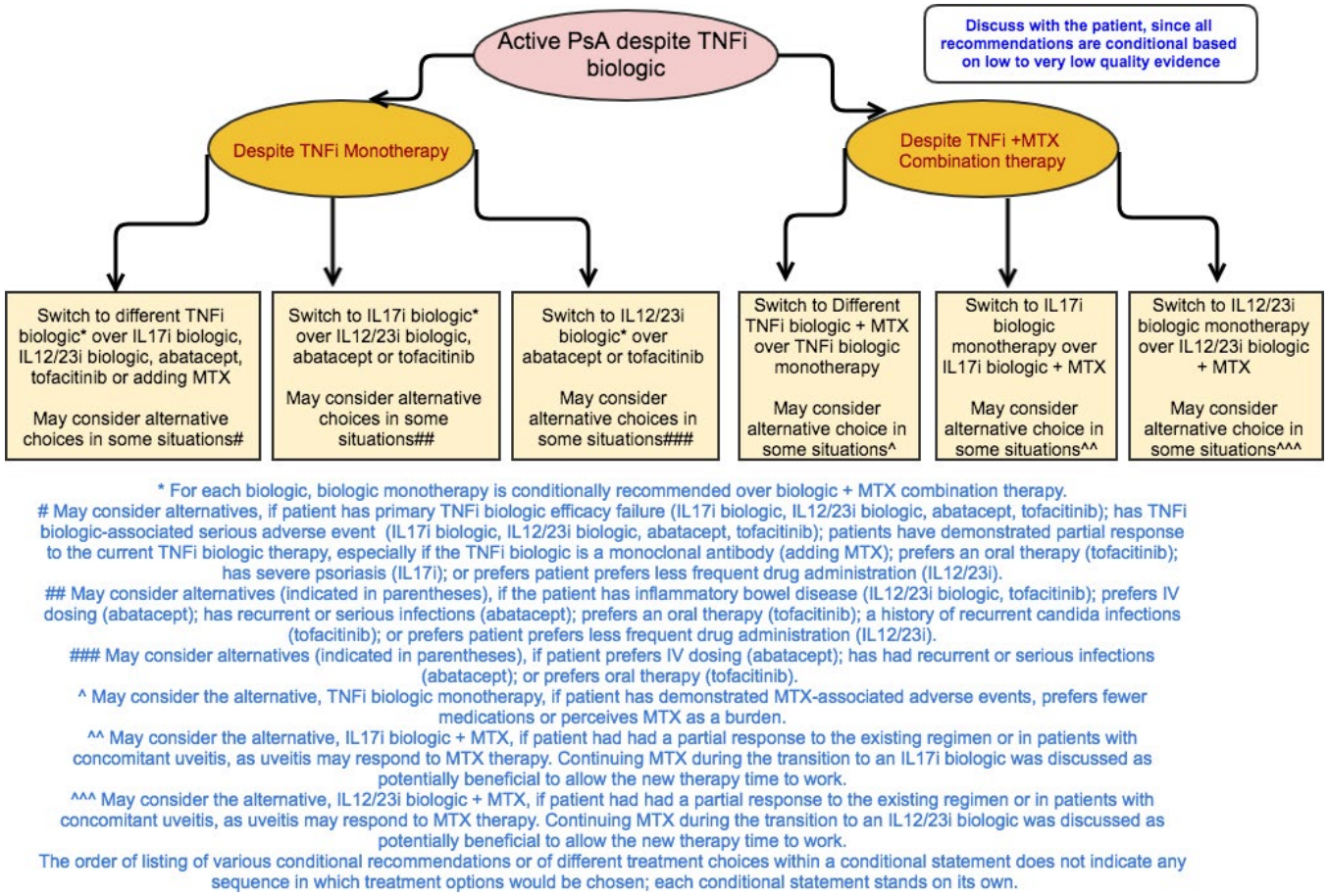
Active PsA despite TNFi biologic
Discuss with the patient, since all recommendations are conditional based on low to very low quality evidence
Despite TNFi Monotherapy
Despite TNFi +MTX Combination therapy
Switch to different TNFi biologic* over IL17i biologic, IL12/23i biologic, abatacept, tofacitinib or adding MTX
May consider alternative choices in some situations#
Switch to IL17i biologic* over IL12/23i biologic, abatacept or tofacitinib
May consider alternative choices in some situations##
Switch to IL12/23i biologic* over abatacept or tofacitinib
May consider alternative choices in some situations###
Switch to Different TNFi biologic + MTX over TNFi biologic monotherapy
May consider alternative choice in some situations^
Switch to IL17i biologic monotherapy over IL17i biologic + MTX
May consider alternative choice in some situations^^
Switch to IL12/23i biologic monotherapy over IL12/23i biologic + MTX
May consider alternative choice in some situations^^^
* For each biologic, biologic monotherapy is conditionally recommended over biologic + MTX combination therapy.
# May consider alternatives, if patient has primary TNFi biologic efficacy failure (IL17i biologic, IL12/23i biologic, abatacept, tofacitinib); has TNFi biologic-associated serious adverse event (IL17i biologic, IL12/23i biologic, abatacept, tofacitinib); patients have demonstrated partial response to the current TNFi biologic therapy, especially if the TNFi biologic is a monoclonal antibody (adding MTX); prefers an oral therapy (tofacitinib); has severe psoriasis (IL17i); or prefers patient prefers less frequent drug administration (IL12/23i).
May consider alternatives (indicated in parentheses), if the patient has inflammatory bowel disease (IL12/23i biologic, tofacitinib); prefers IV dosing (abatacept); has recurrent or serious infections (abatacept); prefers an oral therapy (tofacitinib); a history of recurrent candida infections (tofacitinib); or prefers patient prefers less frequent drug administration (IL12/23i).
May consider alternatives (indicated in parentheses), if patient prefers IV dosing (abatacept); has had recurrent or serious infections (abatacept); or prefers oral therapy (tofacitinib).
^ May consider the alternative, TNFi biologic monotherapy, if patient has demonstrated MTX-associated adverse events, prefers fewer medications or perceives MTX as a burden.
^^ May consider the alternative, IL17i biologic + MTX, if patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL17i biologic was discussed as potentially beneficial to allow the new therapy time to work.
^^^ May consider the alternative, IL12/23i biologic + MTX, if patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL12/23i biologic was discussed as potentially beneficial to allow the new therapy time to work.
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

Figure 5. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with a tumor necrosis factor inhibitor (TNFi) as monotherapy or as combination therapy with methotrexate (MTX). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 3 and the related section in the Results. IL-17i = interleukin-17 inhibitor; IV = intravenous.

if the patient had a partial response to the existing regimen and/or has concomitant uveitis that might respond to MTX therapy.

Active PsA despite treatment with an IL-17i biologic agent as monotherapy (Table 4 and Figure 6). *All recommendations for patients with active PsA despite IL-17i biologic treatment are conditional based on very-low-quality evidence.*

In patients with active PsA despite treatment with an IL-17i biologic, switching to a TNFi biologic is recommended over switching to an IL-12/23i biologic, adding MTX to the current IL-17i biologic, or switching to a different IL-17i biologic (Table 4 and Figure 6). Switching to an IL-12/23i biologic is recommended over adding MTX to the current IL-17i biologic or switching to a different IL-17i biologic. Treatment may be switched to an IL-12/23i biologic instead of a TNFi biologic if the patient has severe psoriasis or a contraindication to TNFi biologic treatment. Another IL-17i biologic may be used instead of switching to a TNFi or IL-12/23i biologic if the patient had a secondary efficacy failure with the current IL-17i biologic, severe psoriasis, or a contraindication to TNFi treatment. MTX may be added to the current IL-17i regimen instead of switching to a TNFi or IL-12/23i biologic in patients who have had a partial response to the current IL-17i biologic.

Active PsA despite treatment with an IL-12/23i biologic agent as monotherapy (Table 4 and Figure 6). *All recommendations for patients with active PsA despite IL-12/23i biologic treatment are conditional based on very-low-quality evidence.*

In patients with active PsA despite treatment with an IL-12/23i biologic, switching to a TNFi biologic is recommended over adding MTX to the current regimen or switching to an IL-17i biologic

Table 4. Recommendations for treatment of patients with active psoriatic arthritis despite treatment with an IL-17i or an IL-12/23i biologic monotherapy (PICOs 36–43)*

	Level of evidence†
In adult patients with active PsA despite treatment with an IL-17i biologic monotherapy,	
1. **Switch to a TNFi biologic over switching to an IL-12/23i biologic** (PICO 39) **Conditional recommendation** based on very-low-quality-evidence; may consider switching to IL- 12/23i if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.	Very low
2. **Switch to a TNFi biologic over switching to a different IL-17i biologic** (PICO 42) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different IL-17i if the patient had had a secondary efficacy failure to current IL-17i, or severe psoriasis, or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
3. **Switch to a TNFi biologic over adding MTX to an IL-17i biologic** (PICO 41) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX to an IL-17i if the patient had had a partial response to the existing regimen or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
4. **Switch to an IL-12/23i biologic over switching to a different IL-17i biologic** (PICO 43) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different IL-17i if the patient had had a secondary efficacy failure to current IL-17i or severe psoriasis,‡ or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
5. **Switch to an IL-12/23i biologic over adding MTX to an IL-17i biologic** (PICO 40) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX to an IL-17i if the patient had had a partial response to the existing regimen.	Very low
In adult patients with active PsA despite treatment with an IL-12/23i biologic monotherapy,	
6. **Switch to a TNFi biologic over switching to an IL-17i biologic** (PICO 38) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i if the patient has severe psoriasis or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
7. **Switch to a TNFi biologic over adding MTX to an IL-12/23i biologic** (PICO 36) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX in patients in whom the severe psoriasis is not responding to the current therapy, or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
8. **Switch to an IL-17i biologic over adding MTX to an IL-12/23i biologic** (PICO 37). **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX in patients with only partial response to the current therapy or in those who potentially have not had enough time to adequately respond.	Very low

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease. IL-17i = interleukin-17 inhibitor; TNFi = tumor necrosis factor inhibitor; MTX = methotrexate.

† When there were no published studies—as was the case with all of the recommendations presented in this table—we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

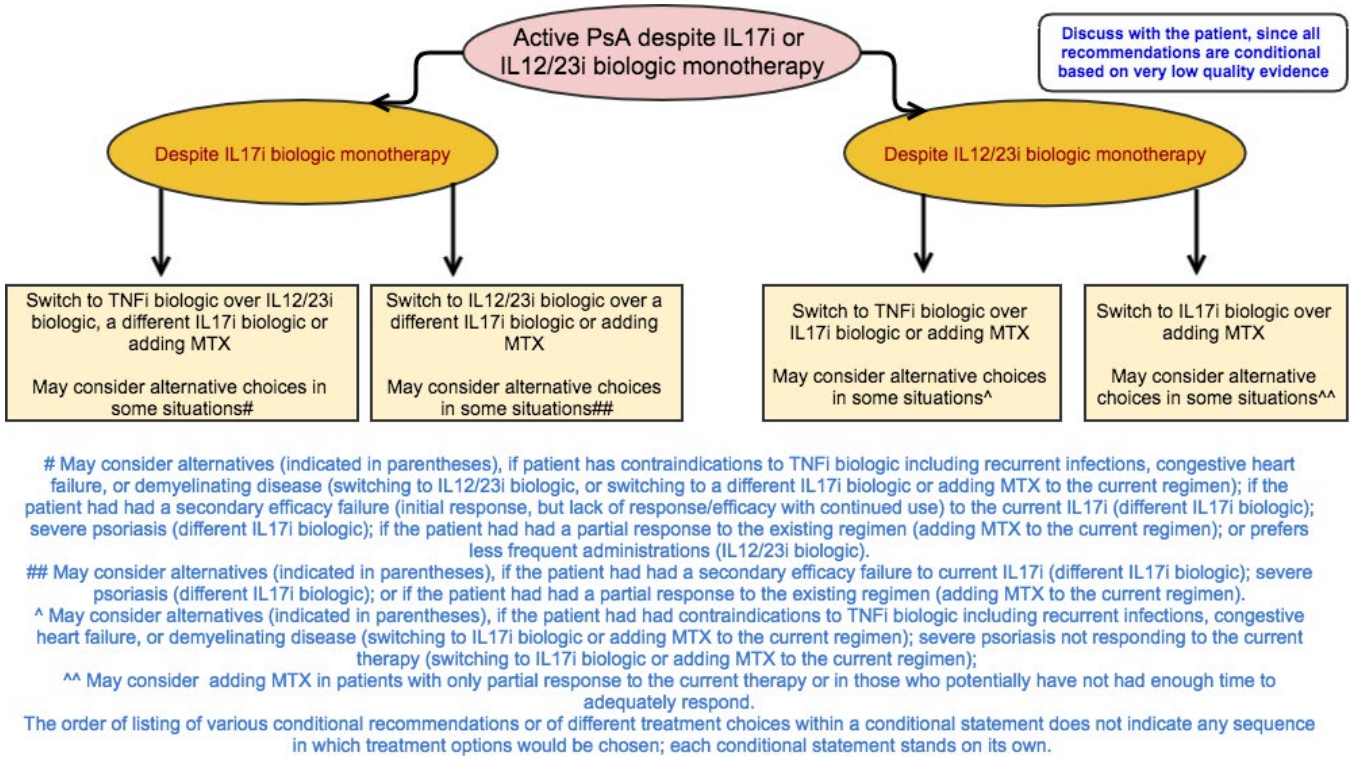
Active PsA despite IL17i or IL12/23i biologic monotherapy
Discuss with the patient, since all recommendations are conditional based on very low quality evidence
Despite IL17i biologic monotherapy
Despite IL12/23i biologic monotherapy
Switch to TNFi biologic over IL12/23i biologic, a different IL17i biologic or adding MTX
May consider alternative choices in some situations#
Switch to IL12/23i biologic over a different IL17i biologic or adding MTX
May consider alternative choices in some situations##
Switch to TNFi biologic over IL17i biologic or adding MTX
May consider alternative choices in some situations^
Switch to IL17i biologic over adding MTX
May consider alternative choices in some situations^^
May consider alternatives (indicated in parentheses), if patient has contraindications to TNFi biologic including recurrent infections, congestive heart failure, or demyelinating disease (switching to IL12/23i biologic, or switching to a different IL17i biologic or adding MTX to the current regimen); if the patient had had a secondary efficacy failure (initial response, but lack of response/efficacy with continued use) to the current IL17i (different IL17i biologic); severe psoriasis (different IL17i biologic); if the patient had had a partial response to the existing regimen (adding MTX to the current regimen); or prefers less frequent administrations (IL12/23i biologic).
May consider alternatives (indicated in parentheses), if the patient had had a secondary efficacy failure to current IL17i (different IL17i biologic); severe psoriasis (different IL17i biologic); or if the patient had had a partial response to the existing regimen (adding MTX to the current regimen).
^ May consider alternatives (indicated in parentheses), if the patient had had contraindications to TNFi biologic including recurrent infections, congestive heart failure, or demyelinating disease (switching to IL17i biologic or adding MTX to the current regimen); severe psoriasis not responding to the current therapy (switching to IL17i biologic or adding MTX to the current regimen);
^^ May consider adding MTX in patients with only partial response to the current therapy or in those who potentially have not had enough time to adequately respond.
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

Figure 6. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with interleukin-17 inhibitor (IL-17i) or IL-12/23i biologic monotherapy. All recommendations are conditional based on low- to very-low-quality of evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 4 and the related section in the Results. TNFi = tumor necrosis factor inhibitor; MTX = methotrexate.

(Table 4 and Figure 6). Switching to an IL-17i biologic is recommended over adding MTX to the current therapy. Treatment may be switched to an IL-17i biologic instead of a TNFi biologic if the patient has severe psoriasis or a contraindication to TNFi biologic treatment. MTX may be added to the current IL-12/23i biologic therapy instead of switching to a TNFi or an IL-17i biologic in patients with a partial response to the current therapy; MTX may also be added to the current IL-12/23i biologic therapy instead of switching to a TNFi biologic in the presence of contraindications to TNFi biologics.

Treat-to-target (Table 5). *This recommendation for patients with active PsA is conditional based on low-quality evidence.*

In patients with active PsA, using a treat-to-target strategy is recommended over not following a-treat-to-target strategy. One may consider not using a treat-to-target strategy in patients in whom there are concerns related to increased adverse events, costs of therapy, and patient burden of medications associated with tighter control.

Active PsA with psoriatic spondylitis/axial disease despite treatment with NSAIDs (Table 5). *All recommendations for patients with active PsA with psoriatic spondylitis/axial disease despite NSAID treatment are conditional based on very-low-quality evidence.*

The ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for patients with axial spondyloarthritis (35) should be followed for patients with axial PsA. OSMs are not effective for axial disease (35). In patients with active axial PsA despite NSAID treatment, a TNFi biologic is recommended over an IL-17i or IL-12/23i biologic, and an IL-17i biologic is recommended over an IL-12/23i biologic. An IL-17i biologic may be used instead of a TNFi biologic if the patient has severe psoriasis or a contraindication to TNFi biologic treatment (Table 5). We recommend *not using* an IL-12/23i biologic since 3 randomized trials of an IL-12/23i biologic (ustekinumab) in patients with axial spondyloarthritis (a related condition) were stopped because the key primary and secondary end points were not achieved (36–38); the safety profile was reportedly consistent with that observed in past ustekinumab studies.

Table 5. Recommendations for treatment of patients with active psoriatic arthritis including treat-to-target, active axial disease, enthesitis, or active inflammatory bowel disease (PICOs 44–55; 58–62)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA,	
1. **Use a treat-to-target strategy over not following a treat-to-target strategy** (PICO 44) **Conditional recommendation** based on low-quality evidence; may consider not following a treat-to-target strategy in patients in whom higher frequency and/or severity of adverse events, higher cost of therapy, or higher patient burden of medications with tighter control are a concern.	Low (113)
In patients with active PsA with psoriatic spondylitis/axial disease despite treatment with NSAIDs,‡	
2. **Switch to a TNFi biologic over switching to an IL-17i biologic** (PICO 46) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-17i biologic if the patient has contraindications to TNFi biologics, congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or if the patient has severe psoriasis.§	Very low
3. **Switch to a TNFi biologic over switching to an IL-12/23i biologic** (PICO 45) **Conditional recommendation** based on very-low-quality evidence; switching to an IL-12/23i biologic is *not* considered since recent trials in axial SpA were stopped.	Very low
4. **Switch to an IL-17i biologic over switching to an IL-12/23i** (PICO 47) **Conditional recommendation** based on very-low-quality evidence; switching to an IL-12/23i biologic is *not* considered since recent trials in axial SpA were stopped.	Very low
In adult patients with active PsA and predominant enthesitis who are both OSM- and biologic treatment–naive,¶	
5. **Start oral NSAIDs over an OSM (specifically apremilast)** (PICO 48) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM (specifically apremilast) if the patient has active joint disease and/or skin disease or contraindications to the use of NSAIDs, including cardiovascular disease, peptic ulcer disease, or renal disease or impairment.	Very low
6. **Start a TNFi biologic over an OSM (specifically apremilast)** (PICO 48A) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM (specifically apremilast) if the patient prefers an oral treatment as the first therapy or the patient has contraindications to TNFi biologics, including recurrent infections, congestive heart failure, or demyelinating disease.	Very low
7. **Start tofacitinib over an OSM (specifically apremilast)** (PICO 55) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM (specifically apremilast) if the patient has recurrent infections.	Very low
In adult patients with active PsA and predominant enthesitis despite treatment with OSM,	
8. **Switch to a TNFi biologic over an IL-17i biologic** (PICO 53) **Conditional recommendation** based on low-quality evidence; may consider switching to an IL-117i if the patient has severe psoriasis or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (72, 73, 76, 89, 90, 92)
9. **Switch to a TNFi biologic over an IL-12/23i biologic** (PICO 52) **Conditional recommendation** based on low-quality evidence; may consider switching to an IL-12/23i if the patient has severe psoriasis or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or if the patient prefers less frequent drug administration.	Low (72, 73, 76, 98, 100)
10. **Switch to a TNFi biologic over switching to another OSM** (PICO 49) **Conditional recommendation** based on low-quality evidence; may consider switching to another OSM# if the patient prefers an oral medication over an injection, or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (72, 73, 76, 83–85)

Table 5. *(Cont'd)*

	Level of evidence (evidence [refs.] reviewed)†
11. **Switch to an IL-17i biologic over an IL-12/23i biologic** (PICO 54) **Conditional recommendation** based on low-quality evidence; may consider switching to an IL-12/23i if the patient has concomitant IBD or if the patient prefers less frequent drug administration.	Low (89, 90, 92, 93, 98–100)
12. **Switch to an IL-17i biologic over switching to another OSM** (PICO 51) **Conditional recommendation** based on low-quality evidence; may consider switching to another OSM if the patient prefers an oral medication.	Low (83–86, 89, 90, 92, 93)
13. **Switch to an IL-12/23i biologic over switching to another OSM** (PICO 50) **Conditional recommendation** based on low-quality evidence; may consider switching to another OSM# if the patient prefers an oral medication over an injection, or if there are contraindications to an IL- 12/23i, such as severe recurrent infections.	Low (83–86, 98, 100)
In adult patients with active PsA and concomitant active IBD who are both OSM- and biologic treatment–naive,	
14. **Start a monoclonal antibody TNFi biologic over an OSM** (PICO 62) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM if the patient prefers an oral medication, or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low (114)
In adult patients with active PsA and concomitant active IBD despite treatment with an OSM,	
15. **Switch to a monoclonal antibody TNFi biologic over a TNFi biologic soluble receptor biologic (i.e., etanercept)** (PICO 58)	Moderate (115–117)
Strong recommendation supported by moderate-quality evidence, showing TNFi monoclonal antibody biologics are effective in IBD but indirect evidence shows a TNFi biologic soluble receptor biologic is not effective for the treatment of IBD.	
16. **Switch to a TNFi monoclonal antibody biologic over an IL-17i biologic** (PICO 59)	Moderate (50)
Strong recommendation supported by moderate-quality evidence showing monoclonal antibody TNFi biologics are effective for IBD while an IL-17i biologic is not effective for IBD.	
17. **Switch to a TNFi biologic monoclonal antibody biologic over an IL-12/23i biologic** (PICO 61) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL- 12/23i biologic if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.	Very low
18. **Switch to an IL-12/23i biologic over switching to an IL-17i biologic** (PICO 60)	Moderate (50)
Strong recommendation supported by moderate-quality evidence showing IL-12/23i biologic is effective for IBD while an IL-17i biologic is not effective for IBD.	

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD).
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Axial disease is generally treated according to the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for spondyloarthritis (SpA).
§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.
¶ Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine, or apremilast and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. OSM- and biologic treatment–naive is defined as naive to treatment with OSMs, tumor necrosis factor inhibitors (TNFi,), interleukin-17 inhibitors (IL-17i), and IL-12/23i; patients may have received nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, and/or other pharmacologic and nonpharmacologic interventions.
# It should be noted that for the enthesitis questions (PICO 49, 50, and 51), the existing evidence was mainly drawn from the apremilast studies, as no randomized controlled trial report described enthesitis outcomes for the other OSMs.

Active PsA with predominant enthesitis in treatment-naive patients and despite treatment with an OSM (Table 5). *All recommendations for patients with active PsA with predominant enthesitis are conditional based on low- to very-low-quality evidence. (This section names apremilast among all OSMs specifically for recommendations, since of the OSMs, only apremilast has shown efficacy for enthesitis.)*

In treatment-naive PsA patients with predominant enthesitis, a TNFi biologic is recommended over an OSM as a first-line option. Apremilast may be used instead of a TNFi biologic if the patient prefers an oral therapy or has contraindications to TNFi. Oral NSAIDs are recommended over starting an OSM unless the patient has cardiovascular disease, peptic ulcer disease, renal disease (or impairment), or severe psoriasis or PsA, in which case apremilast may be given instead of NSAIDs. Tofacitinib is recommended over apremilast for treatment-naive patients with predominant enthesitis. Apremilast may be used instead of tofacitinib in patients with recurrent infections.

In patients with active PsA with predominant enthesitis despite treatment with an OSM (used for other manifestations of PsA), a TNFi biologic, an IL-17i biologic, or an IL-12/23i biologic is recommended over switching to another OSM. Apremilast may be used in patients who prefer oral therapy or who have recurrent infections or contraindications to TNFi biologics. A TNFi biologic is recommended over an IL-17i or IL-12/23i biologic. An IL-17i or IL-12/23i biologic may be used instead of a TNFi biologic in patients with severe psoriasis or contraindications to TNFi. An IL-17i biologic is recommended over an IL-12/23i biologic. An IL-12/23i biologic may be used instead of a TNFi biologic in patients who prefer less frequent drug administration, and instead of an IL-17i biologic in patients with concomitant IBD or who prefer less frequent drug administration.

Active PsA with concomitant active IBD (Table 5). *All recommendations for patients with active PsA with concomitant active IBD are strong based on moderate-quality evidence, except for 2 conditional recommendations based on very-low-quality evidence.*

Active PsA in OSM- and biologic treatment–naive patients with concomitant active IBD. In patients with active PsA with concomitant active IBD who have not received OSM or biologic treatment, a monoclonal antibody TNFi biologic (excludes etanercept, which is a fusion molecule/soluble receptor biologic) is recommended over an OSM (Table 5). An OSM may be used in patients without severe PsA who prefer oral therapy or have contraindications to TNFi biologics.

Active PsA despite treatment with an OSM in patients with concomitant active IBD. In patients with active PsA with concomitant active IBD despite treatment with an OSM, a monoclonal antibody TNFi biologic or an IL-12/23i biologic *should be used* over an IL-17i biologic, and a monoclonal antibody TNFi biologic *should be used* over a TNFi soluble receptor biologic (etanercept) (*all strong recommendations* [Table 5]). A monoclonal antibody TNFi biologic is recommended over an IL-12/23i biologic (conditional recommendation). An IL-12/23i biologic may be used instead of a monoclonal antibody TNFi biologic in patients with contraindications to TNFi biologics or who prefer less frequent drug administration.

Active PsA with comorbidities (Table 6). *All recommendations for patients with active PsA with comorbidities are conditional based on low- to very-low-quality evidence, except those for patients with serious infections, which are strong based on moderate-quality evidence.*

Active PsA in OSM- and biologic treatment–naive patients with concomitant diabetes. In patients with active PsA with concomitant active diabetes who have not received OSM or biologic treatment, an OSM other than MTX is recommended over a TNFi biologic, due to the concern about the higher prevalence of fatty liver disease and liver toxicity with MTX use in this patient population (39,40) (Table 6). A TNFi biologic may be used instead of an OSM in the presence of severe PsA or severe psoriasis or when diabetes is well controlled (i.e., with a potentially lower risk of infections).

Active PsA in OSM- and biologic treatment–naive patients with frequent serious infections. In patients with active PsA who have frequent serious infections and have not received OSM or biologic treatment, an OSM *should be used* over a TNFi biologic as a first-line treatment since there is a black box warning against the use of a TNFi biologic in patients with frequent serious infections (*strong recommendation*). An IL-12/23i or IL-17i biologic is recommended over a TNFi biologic (conditional recommendation [Table 6]). A TNFi biologic may be used instead of an IL-12/23i biologic in patients with severe PsA and instead of an IL-17i biologic in patients with concomitant IBD.

Active PsA in patients requiring killed or live attenuated vaccinations when starting biologic treatment (Table 7). *All recommendations for vaccinations in patients with active PsA are conditional based on very-low-quality evidence.*

It is recommended that the biologic treatment be started and the killed vaccines administered (as indicated based on patient age, sex, and immunization history per recommendations of the Centers for Disease Control and Prevention [41]) in patients with active PsA over delaying the biologic to give the killed vaccines. Delaying the start of the biologic is recommended over not delaying to administer a live attenuated vaccination in patients with active PsA (Table 7). If PsA manifestations are severe and delaying the start of the biologic is not desirable, starting the biologic and administering the live attenuated vaccines at the same time might be considered.

Table 6. Recommendations for treatment of patients with active psoriatic arthritis and comorbidities, including concomitant diabetes and recurrent serious infections (PICOs 63–66)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA and diabetes who are both OSM- and biologic treatment–naive,‡	
1. **Start an OSM other than MTX over a TNFi biologic** (PICO 63a) **Conditional recommendation** based on very-low-quality evidence; may consider starting a TNFi, if the patient has severe PsA§ or severe/active skin disease,¶ when diabetes is well controlled.	Very low (118, 119)
In adult patients with active PsA and frequent serious infections who are both OSM- and biologic treatment–naive,	
2. **Start an OSM over a TNFi biologic** (PICO 64) **Strong recommendation** supported by moderate-quality evidence, including a black box warning against the use of a TNFi biologic with regard to increased risk of serious infection.	Moderate (33, 120)
3. **Start an IL-12/23i biologic over a TNFi biologic** (PICO 65) **Conditional recommendation** based on very-low-quality evidence; may consider starting a TNFi if the patient has severe PsA.	Very low (33)
4. **Start an IL-17i biologic over a TNFi biologic** (PICO 66) **Conditional recommendation** based on very-low-quality evidence; may consider starting a TNFi biologic in patients with concomitant IBD.	Very low

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD).
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine, or apremilast and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. OSM- and other treatment–naive is defined as naive to treatment with OSMs, tumor necrosis factor inhibitors (TNFi), interleukin-17 inhibitors (IL-17i), and IL-12/23i; patients may have received nonsteroidal antiinflammatory drugs, glucocorticoids, and/or other pharmacologic and nonpharmacologic interventions.
§ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.
¶ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

Recommendations for nonpharmacologic interventions in patients with active PsA regardless of pharmacologic treatment status (Table 8)

All recommendations for nonpharmacologic interventions for patients with active PsA are conditional based on low- to very-low-quality evidence, except that for smoking cessation, which is a strong recommendation.

It is recommended that patients with active PsA use some form or combination of exercise, physical therapy, occupational therapy, massage therapy, and acupuncture over not using these modalities as tolerated. Low-impact exercise (e.g., tai chi, yoga, swimming) is recommended over high-impact exercise (e.g., running). High-impact exercises may be performed instead of low-impact exercises by patients who prefer the former and

Table 7. Recommendations for vaccination in patients with active psoriatic arthritis (PICOs 56–57)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA needing vaccinations,‡	
1. **Start the biologic and administer killed vaccines over delaying the start of biologic to administer killed vaccines** (PICO 56) **Conditional recommendation** based on very-low-quality evidence; may consider delaying the start of biologic to administer killed vaccines due to patient preference based on patient belief about vaccine efficacy.	Very low (121–126)
2. **Delay the start of biologic to administer live attenuated vaccines over starting the biologic and administering live attenuated vaccines** (PICO 57) **Conditional recommendation** based on very-low-quality evidence; may consider starting the biologic and administering live attenuated vaccines in patients with very active severe joint§ or skin¶ disease who prefer no delay in biologic initiation.	Very low (127)

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Vaccines as indicated by patient age, sex, and immunization history per recommendations from the Centers for Disease Control and Prevention and available at: https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf.
§ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.
¶ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

have no contraindications to high-impact exercises (Table 8). Clinicians *should* encourage patients to stop smoking, offering cessation aids, due to a demonstrated effectiveness of smoking cessation in randomized trials in other conditions and in the general population (42–44) (*strong recommendation*). In PsA patients who are overweight or obese, weight loss is recommended in order to potentially increase pharmacologic response.

All strong recommendations in this guideline are also listed separately in Supplementary Appendix 6, at http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract.

DISCUSSION

We present herein the first ACR/NPF guideline for the treatment of psoriatic arthritis. The goal of this guideline is to assist health care providers in managing active PsA in their patients, including optimizing therapy. PsA is a heterogeneous and multifaceted inflammatory disease, and its different clinical features (e.g., peripheral arthritis, psoriasis, nail disease, enthesitis, dactylitis, axial disease) sometimes respond differently to therapy. Despite an expansion in the number of new therapies for PsA, there remains limited comparative efficacy/effectiveness evidence to inform treatment decisions. Thus, most of our recommendations are based on low-quality evidence and are conditional. The conditional recommendations convey that, although the suggested course of action will be best for many patients, there will be some patients in whom, considering their comorbidities and/or their values and preferences, the alternative represents the best choice. The guideline will be updated as new evidence from comparative studies becomes available.

A Patient Panel meeting was held prior to the Voting Panel meeting to gain insight into patients' values and preferences for the pharmacologic/nonpharmacologic intervention comparisons being addressed. We recognize that patient preferences are an important part of our treatment recommendations. Findings from the Patient Panel meeting were discussed throughout the Voting Panel

Table 8. Recommendations for treatment of patients with active psoriatic arthritis with nonpharmacologic interventions (PICOs 1–8)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA,	
1. **Recommend exercise over no exercise** (PICO 1) **Conditional recommendation** based on low-quality evidence; may consider no exercise in patients with existing muscle/tendon injury or multiple inflamed symptomatic joints with worsening pain with exercise.	Low (128)
2. **Recommend low-impact exercise (e.g., tai chi, yoga, swimming) over high-impact exercise (e.g., running)** (PICO 2) **Conditional recommendation** based on very-low-quality evidence; may consider high-impact exercise due to patient preference.	Very low
3. **Recommend physical therapy over no physical therapy** (PICO 3) **Conditional recommendation** based on very-low-quality evidence; may consider no physical therapy due to patient preference, out-of-pocket cost, distance to physical therapy site, or lack of transportation.	Very low
4. **Recommend occupational therapy over no occupational therapy** (PICO 4) **Conditional recommendation** based on low-quality evidence; may consider no occupational therapy due to patient preference, out-of-pocket cost, distance to occupational therapy site, or lack of transportation.	Low (129, 130)
5. **Recommend weight loss over no weight loss for patients who are overweight/obese** (PICO 5) **Conditional recommendation** based on low-quality evidence; may consider no weight loss due to additional patient burden involved with weight-loss program.	Low (131–133)
6. **Recommend massage therapy over no massage therapy** (PICO 7) **Conditional recommendation** based on very-low-quality evidence; may consider no massage therapy due to associated costs.	Very low (134)
7. **Recommend acupuncture over no acupuncture** (PICO 8) **Conditional recommendation** based on very-low-quality evidence; may consider no acupuncture due to associated costs.	Very low (135)
8. **Recommend smoking cessation over no smoking cessation** (PICO 6) **Strong recommendation** supported by moderate-quality evidence, rated down for indirectness.	Moderate (136, 137)

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

meeting to ensure that patient input was incorporated into the final PsA guideline. Examples of patient feedback included strong value on therapies that are effective (e.g., prevent further damage, and improve quality of life, social participation, and function) and safe (especially having low adverse event profiles). In particular, patients discussed the negative impact of adverse events (e.g., fatigue, nausea, and malaise) on quality of life and social participation, and thus the risk for these adverse events weighed heavily in patients' decision-making. The concept of treat-to-target was challenging for patients. Although they saw value in improved outcomes, they also thought this strategy could increase costs to the patient (e.g., copayments, time traveling to more frequent appointments, etc.) and potentially increase adverse events. Therefore, a detailed conversation with the patient is needed to make decisions regarding treat-to-target. To help ensure that the recommendations were patient-centered, 2 patients were members of the Voting Panel.

While using a treat-to-target approach over not using a treat-to-target approach was discussed by the Voting Panel, we did not address specific targets to be recommended or used. There have been 2 international meetings to discuss potential targets: the use of either minimal disease activity (MDA) or disease activity in psoriatic arthritis (DAPSA) (45,46). The treatment target for PsA would likely be MDA or DAPSA, although a different target may be chosen through patient–provider discussion.

The ACR/NPF PsA guideline conditionally recommends a TNFi biologic over an OSM agent in patients with active PsA. The

available low-quality evidence is inconclusive regarding the efficacy of OSMs in management of PsA, whereas there is moderate-quality evidence of the benefits of TNFi biologics, in particular regarding their impact on the prevention of disease progression and joint damage. In making their recommendation, the panel recognized the cost implications, but put considerations of quality of evidence for benefit over other considerations. This guideline provides recommendations for early and aggressive therapy in patients with newly diagnosed PsA.

The recommendation is, however, conditional, and the panel recognized several potential exceptions to it. Circumstances in which a patient may choose an OSM over a TNFi biologic may include mild-to-moderate disease, a preference of oral over parenteral therapy, or concerns regarding adverse effects of a biologic. A TNFi biologic would not be a good choice in patients with contraindications, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.

During the development of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommendations (47) and the European League Against Rheumatism (EULAR) recommendations (48) for the treatment of PsA, panel members also challenged the decision to put OSMs first in those recommendations. For the EULAR recommendations, the final decision was made based on the lower cost of these medications, a consideration our panel placed lower than the quality of evidence for benefit.

In patients with concomitant IBD, the Voting Panel made strong recommendations favoring a monoclonal antibody TNFi or an IL-12/23i biologic over an IL-17i biologic or a TNFi receptor biologic (etanercept). This was based on moderate-quality evidence showing that TNFi biologics and ustekinumab (an IL-12/23i biologic) are effective for the management of IBD, whereas etanercept (a TNFi receptor biologic) and secukinumab (an IL-17i biologic) are not (49,50).

When the evidence was low or very-low quality, the panel could not be confident in the judgment of net benefit—thus the conditional recommendation. Often, low- or very-low-quality evidence came from indirect evidence, for instance from rheumatoid arthritis (33) or, in the absence of studies, from clinical experience (Supplementary Appendix 5, on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract). When data on comparative benefits and comparative harms were similar between two medications, the panel explicitly preferred and recommended the medication for which longer-term harms were more well-known, and in which the physician experience in patients with PsA was longer, supplementing with harms data/experience from related rheumatic conditions, where these medications are commonly used. In each case, judgments of net benefit involved explicit consideration of values and preferences, including input from Patient Panel members of the Voting Panel as well as the full Patient Panel that met prior to the Voting Panel meeting.

We recognize that these recommendations do not account for the full complexity of PsA or the full range of possible therapies (e.g., glucocorticoids were not addressed). The high degree of heterogeneity in the presentation and course of PsA coupled with the involvement of multiple domains in a single patient cannot be captured in a single algorithm. In addition, reporting of disease measures and differences in inclusion/exclusion criteria in PsA clinical trials makes it difficult to compare therapies across trials. The impact of alternative therapies on important outcomes such as joint damage still remains to be elucidated. Vaccination recommendations with tofacitinib were not included, as it was not yet approved for PsA when the PICO questions were drafted and only a limited number of PICO questions could be feasibly included for voting. Additional topics, including vaccination in the setting of tofacitinib, will be addressed in a subsequent guideline update.

The ACR has decided to use GRADE methodology in the development of guidelines for the management of rheumatic diseases. The GRADE methodology specifies that panels make recommendations based on a consideration of the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the evidence based on the lowest quality of the critical outcomes—high, moderate, low, or very low), and patients' values and preferences. The rating of the quality of evidence for each clinical situation (PICO question) helped to inform the strength of the recommendation (strong or conditional) (51).

The use of GRADE (not used in other PsA treatment recommendations) allowed an explicit consideration of the overall evidence, including the balance of benefits and harms of treatments, the incorporation of patient values and preferences, and cost considerations to judge the tradeoff. This approach led to transparency in decision making by the Voting Panel for each clinical scenario and the formulation of these recommendations. Consistent with GRADE guidance, the Voting Panel usually offered a strong recommendation in the presence of moderate- or high-quality rating of the evidence, and a conditional recommendation in the presence of very-low or low-quality evidence (although recommendations can also be conditional in the setting of moderate-quality evidence, and in certain circumstances strong in the face of low-quality evidence) (15). The other merits of the ACR/NPF process undertaken included a comprehensive literature search, the consideration of each comparison in light of the available evidence, the diverse composition of the Voting Panel, the inclusion of all of the available therapies (e.g., IL-17i biologics, an IL-12/23i biologic, abatacept, and tofacitinib) in the decision-making process (including those approved for psoriasis or rheumatoid arthritis but not yet for PsA, ensuring that the guideline would not be out of date by the time it was published), and the inclusion of population subsets, such as those with predominant enthesitis and/or IBD.

Limitations of the guideline include the limited comparative evidence to inform selection of therapies (i.e., primary comparative benefit/efficacy and harms evidence) and the inability to include all possible clinical scenarios due to the necessity of keeping the task feasible. Because the American Academy of Dermatology and the NPF are currently developing a guideline addressing therapy for psoriasis, our guideline did not address treatment of isolated psoriasis. Another limitation is that we searched only English-language literature. The major limitation of the work arises from the limitations in the evidence.

In this guideline, we often used indirect comparisons among trials/therapies, frequently relying on network meta-analysis. Stratified analyses among subgroups (e.g., treatment-naive, inadequate response to a TNFi biologic agent) were rarely reported separately in primary trials, limiting our ability to perform network meta-analyses in these important subgroups. For most clinical scenarios (PICO questions) there were few or no head-to-head comparison studies identified in the literature review. Thus, the quality of evidence was most often low or very low, and only occasionally moderate (Supplementary Appendix 5; http://onlinelibrary.wiley.com/doi/10.1002/art.40726/abstract). This led to nearly all recommendations being conditional, with a few strong recommendations in cases in which there was sufficient evidence (including that from outside of PsA) to make the Voting Panel confident in selecting one option over the comparator. A flow chart or ranking of treatments requires strong recommendation; when recommendations are conditional/weak it means that the right course of action differs between patients. When the right course of action differs between patients, it is inappropriate to make the flow chart and establish treatment ranking or a hierarchy of treatment options (14).

The 2018 ACR/NPF guideline for the treatment of PsA will assist patients and their health care providers in making challenging disease management decisions. More comparative data are needed to inform treatment selection. Several ongoing trials, including a trial to compare a TNFi biologic combination therapy with a TNFi biologic monotherapy and MTX monotherapy (52), will inform treatment decisions. We anticipate future updates to the guideline when new evidence is available.

ACKNOWLEDGMENTS

We thank Ms Emily Boyd with the NPF for her involvement throughout the guideline development process. We thank Dr. Maureen Dubreuil for leading the Patient Panel meeting, as well the patients who participated in this guideline project: Eddie Applegate, Steve Bishkoff, Christy Gephart, Lisa Medlin, Gail C. Richardson, Richard F. Seiden, Delores Teddleton, and Hilary Wilson. We thank the ACR staff, including Ms Regina Parker for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project and Ms Robin Lane for assistance in manuscript preparation. We thank Ms Janet Joyce for help in developing the literature search strategy and performing the literature search and updates, and Ms Tamara Rader for peer-reviewing the literature search strategy. We thank Dr. Jonathan Treadwell for his statistical contributions to the network meta-analyses that were done as part of the literature review.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Singh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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RHEUMATOLOGY

GUIDELINES

British Society for Rheumatology

Rheumatology 2022;61:e255–e266
https://doi.org/10.1093/rheumatology/keac295
Advance access publication 31 May 2022

The 2022 British Society for Rheumatology guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs

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Key words: PsA, biologics, targeted synthetic DMARDs, treatment, management, guideline, recommendations, psoriasis, enthesitis, dactylitis

Background

PsA is a chronic, inflammatory, musculoskeletal disease affecting approximately one quarter of people with the skin condition psoriasis [1, 2]. PsA is a highly heterogeneous disease, encompassing diverse musculoskeletal manifestations or 'domains' resulting from disease activity in different tissues. These include peripheral arthritis, spondylitis (axial inflammation), dactylitis (inflammation of the whole digit) and enthesitis (inflammation where a tendon, ligament or joint capsule insert to the bone). Unlike RA, there is a significant variability in clinical presentation of PsA. Individuals with PsA may have different domains involved and drugs have different levels of effectiveness on each domain. It is therefore essential that clinical guidelines for the treatment selection in PsA include disease phenotype and differential effect of medication.

PsA is a potentially debilitating and destructive disease, with half of people developing irreversible joint damage within 2 years [3]. This results in significant functional limitations, depression and anxiety, as well as negatively impacting on education, work capacity and social participation [4–8]. Furthermore, PsA is associated with extra-articular manifestations, including inflammatory bowel disease (Crohn's disease and ulcerative colitis) and uveitis. In addition, metabolic syndrome (obesity, diabetes, hypertension, hyperlipidaemia, fatty liver disease) and cardiovascular disease are more

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Submitted 1 April 2022; accepted 13 April 2022

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common compared with the prevalence in the general population [7, 9, 10]. All of these factors may influence treatment selection [11] and potentially modifiable risk factors, such as obesity and smoking, which can impact therapeutic response and prognosis, should be addressed within the management plan.

There is strong evidence that a treat-to-target (T2T) approach to PsA management, aiming for remission or low disease activity, results in better clinical, radiographic and patient-reported outcomes [12, 13]. Significant advances in therapeutic options available for PsA now mean a target of remission is an achievable goal. Despite PsA being a highly heterogeneous disease, most physicians apply the same step-up therapy to all people with peripheral arthritis, owing to the lack of comparative evidence. Initially a single conventional systemic disease-modifying anti-rheumatic drug (csDMARD) is used, with methotrexate typically being prescribed first-line. This is followed by use of an alternative single csDMARD or combinations of csDMARDs, prior to biologic use if the previous treatment step is unsuccessful [11, 14]. Up to 50% of people with PsA require biologic or targeted synthetic (b/ts)DMARD therapy [15] and treatment in the UK is governed by specific agencies, owing to the higher cost of these drugs. This includes recommendations in England from the National Institute for Health and Care Excellence (NICE) criteria and in Scotland from the Scottish Medicines Consortium (SMC). In addition, non-steroidal anti-inflammatory drugs and local corticosteroids are frequently used, which although not optimal for long-term use, do offer quick, short-term symptomatic relief, while DMARDs take effect.

In practice, biologics require use for a minimum of 12 (e.g. TNFi) or 16 weeks (e.g. IL-17Ai), before response can be evaluated [16]. Unfortunately, a proportion of people do not respond to the first-line drug chosen (primary non-response), while other people respond well initially, but subsequently lose response (secondary non-response). For these reasons, as well as adverse events encountered by some people, switching therapy is required to achieve and maintain treatment targets.

Need for updating of guideline

The last British Society for Rheumatology (BSR) guideline for the treatment of PsA was published in 2012 [12] and focussed specifically on TNF inhibitors as they were the only biologic DMARDs (bDMARDs) available. Since that time, there have been significant advances in therapeutic options available for PsA and drugs with different modes of action are now available, including IL17, IL12/23, IL23 p19, Cytotoxic T-lymphocyte-Associated antigen 4 (CTLA4-Ig), Phosphodiesterase-4 (PDE4) and Janus kinase (JAK) inhibition (i).

We recognize existing high-quality international treatment recommendations, which include those written by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) in 2021, EULAR in 2020 and American College of Rheumatology in 2018 [13, 17, 18]. However, these are generic to many international health settings and do not provide specific guidance for the UK, taking account of the healthcare system and prescribing restrictions. This guideline aims to look at the evidence beyond current NICE technology appraisals and to provide advice for the management of people with PsA.

Objectives

This guideline offers systematic and evidence-based recommendations to support UK clinicians in the prescription of bDMARD and tsDMARD therapies in adults with PsA. The guideline also includes guidance for managing those patients with extra-articular manifestations [uveitis and inflammatory bowel disease (IBD)], as well as those who smoke or are overweight. The guideline provides a stepwise management plan giving clear advice on treatment, including drug eligibility, sequencing, switching and treatment strategy.

This guideline complements existing BSR guidelines and therefore does not include:

i. detailed assessment of the safety of bDMARDs;
ii. biologic or tsDMARD therapies for juvenile idiopathic arthritis;
iii. use of csDMARDs in PsA;
iv. use of biologics or tsDMARDs in pregnancy; or
v. biologic or tsDMARD therapies for adults with psoriatic disease confined to the skin only (in this situation, please refer to BAD guidelines for management of psoriasis at https://www.bad.org.uk/healthcare-professionals/psoriasis).

Target audience

The guideline has been developed to provide assistance to rheumatologists, dermatologists and other clinicians involved in the prescription of biologics and tsDMARDs for people with PsA. The guideline will also assist specialist nurses and allied health professionals (AHPs) in the assessment of treatment response, drug sequencing and switching and provide information to people with PsA who are receiving or moving towards biologic or tsDMARD therapy.

Stakeholder involvement

The guideline has been developed by a multidisciplinary guideline working group (GWG) set up by BSR, including rheumatologists, dermatologists, an ophthalmologist, a gastroenterologist, a general practitioner, an epidemiologist, a specialist nurse and patient representatives. Any conflicts of interest among the GWG were fully declared. Details of members of this working party and their declared conflicts of interest are included at the end of this article and are available on the BSR website. The guideline was presented for comment at the BSR Annual Meeting in 2022 and was available for open consultation on the BSR website for a month prior to submission for publication. Opinions of key stakeholders, including members of the BSR, and Primary

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Care Rheumatology and Musculoskeletal Medicine Society (PCRMM), as well as patient members of the Psoriasis and Psoriatic Arthritis Alliance (PAPAA), were also sought.

Rigour of development

This guideline and recommendations were developed in line with BSR's Guidelines Protocol [19], which has National Institute for Health and Care Excellence (NICE) accreditation. The guideline and recommendations were underpinned with a systematic literature review.

Literature review

The evidence used to develop this guideline was compiled from a systematic literature review (SLR), including electronic bibliographic databases (Medline and Embase) and the Cochrane Database of Systematic Reviews up to 10 December 2020. Key terms for the search were the following: MeSH terms arthritis, psoriatic, psoriatic arthritis, psoriasis and arthritis in combination (independently) with biologic therapy mode of action, targeted synthetic mode of action or any biologic or tsDMARD drug name. Inclusion criteria for review were clinical outcomes in adults with PsA, published in English or in languages other than English with an English translation available. All titles and abstracts were screened by the BSR systematic literature reviewer and full papers of relevant material were obtained. In addition, data extraction and quality assessment undertaken by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [20] was utilized to aid in the completion of this SLR. Reviews of the articles included were conducted to establish current evidence for the following topics: efficacy of TNF inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, IL-17 inhibitors, abatacept, apremilast or JAK inhibitors in different disease domains (peripheral arthritis, axial disease, enthesitis, dactylitis) as well as extra-articular diseases (psoriasis, uveitis and inflammatory bowel disease), the clinical effectiveness of a treat-to-target strategy, the impact of bDMARD or tsDMARD tapering and dose reduction in remission, switching to a biosimilar drug, use of concomitant csDMARDs, efficacy of biologic and tsDMARD therapies in people who are overweight or smoke and the clinical effects of weight loss and smoking cessation in adults with active PsA. These key questions were agreed by the GWG prior to the literature search and published in the guideline scope [21].

In relation to efficacy, only randomized controlled trials (RCTs) of high quality were included for musculoskeletal and skin features of psoriatic disease, whereas in other areas, given the paucity of published data, wider data were included. Data from relevant articles were extracted using standardized literature evaluation forms in order to summarize evidence. Evidence for all aspects of the guideline was limited to articles published in peer-reviewed medical journals. There is a wealth of evidence concerning efficacy and safety of the bDMARDs and tsDMARDs available in PsA but a limited amount of evidence available to support recommendations on choice of therapy and treatment strategy.

Level of evidence

This guideline was developed in line with BSR's Guidelines Protocol [19]. The GWG convened on five occasions to review evidence and formulate recommendations. A draft document of the guideline was circulated to the full GWG for review. Each suggested recommendation in the final document was evaluated by all members and subjected to a vote relating to strength of agreement on a scale of 1 (total disagreement) to 10 (total agreement). The strength of agreement across the GWG for each recommendation is presented as the mean of the members' individual strength of recommendation, expressed as a percentage (e.g. 100% implies all responses were 10/10). The recommendation statements are presented at the beginning of each section. The GRADE approach to assessing the quality and strength of recommendations was adopted [22]. In addition, and in accordance with the BSR protocol accompanying each recommendation in parenthesis is a statement reflecting the strength of recommendation and quality of supporting evidence.

Strength of the recommendation

A strong recommendation to offer (or not to offer) something, where the benefits clearly outweigh the risks (or vice versa) for nearly all patients, is denoted by the number 1 in the guideline. A conditional recommendation (to consider or not) is made either when the risks and benefits are more closely balanced or are more uncertain and is denoted by the number 2 in this guideline.

Quality of evidence

Assessment of supporting evidence quality in GRADE reflects confidence in the estimates of benefits, harms and burdens. This guideline uses three levels and a letter (A, B, C) to reflect high, moderate or low/very low quality of evidence.

High quality is where further research is very unlikely to change the confidence in the estimate of effect.

Moderate quality is where further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality is where further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low-quality is where any estimate of effect is very uncertain.

Plan for review

The planned review date for this guideline will be in five years' time. However, important interim changes will be updated on the BSR website.

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The guideline

Each of the seven sections of the guideline (overarching recommendations, treatment by disease domain, psoriasis and uveitis, IBD, treatment strategy, prescribing/switching, lifestyle choices) will now be discussed in detail. For each statement, a review of the evidence will follow.

New treatment algorithm

The guideline includes a new and expanded treatment algorithm incorporating all the modes of action available. The algorithm is intended to be practical and accessible 'at a glance' to practicing clinicians. The algorithm is underpinned by the key principle of thorough disease assessment to adequately understand disease phenotype and therefore to facilitate selection of b/tsDMARDs based on the domains of disease. The step-up algorithm incorporates the treat-to-target approach, the importance of considering comorbidities and associated conditions. See Fig. 1 for the new treatment algorithm.

Overarching generic recommendations and levels of agreement

GRADE recommends that where it is generally agreed by the medical community that certain principles of diagnosis and disease will do more good than harm (or vice versa), then these should be stated in terms of 'good practice statements' or generic recommendations [23]. The generic recommendations within this guideline are not necessarily evidence-based; however, they are a description of generally accepted best medical practice agreed within our GWG.

i. Therapeutic decisions need to be individualized and should be based on shared decision making between people with psoriatic arthritis and their clinicians [strength of agreement (SoA) 98%].
ii. All medication decisions in people with PsA should take into account: disease presentation with activity in the different domains below, previous medication use, associated conditions such as psoriasis, uveitis and IBD, other comorbidities and patient preference (SoA 97%).
iii. When a range of clinically suitable and equivalent treatments are being considered by people with psoriatic arthritis and their clinicians, select the least expensive, taking into account administration costs, dosage, price per dose and commercial arrangements (SoA 88%).
iv. If people with PsA have an inadequate response to a b/tsDMARD, consider potential factors that could be addressed including: confirming correct diagnosis, adherence, pain due to other causes, drug levels and immunogenicity (SoA 95%).

While discussions about treatments may be discussed with wider members of the rheumatology team, we suggest that commencing a bDMARD or tsDMARD for PsA remains a decision that should be made by a rheumatology consultant.

Treatment by domains

Peripheral arthritis (mono-, oligo- and polyarthritis)

i. In people with active psoriatic arthritis (defined as at least three tender and three swollen joints or those with fewer joints and either poor prognostic markers or severe disease impact defined as $\geq$2 domains involved, extraarticular involvement or impaired quality of life), with inadequate response or intolerance to one csDMARD, consider escalation to b/tsDMARDs (GRADE 2A, SoA 98%).

This recommendation refers to people with active peripheral PsA (at least three tender and three swollen joints or those with fewer joints but severe disease impact), with an inadequate response or intolerance to a csDMARD (methotrexate, leflunomide, sulfasalazine). In these individuals, escalation to a b/tsDMARD should be considered. This eligibility recommendation was made through group consensus and would bring the UK in line with the majority of European healthcare settings. However, the use of biologics after one csDMARD or for people with less than three tender/swollen joints is not currently permitted by NICE TAGs. A full assessment of evidence for csDMARD effectiveness was beyond the scope of this guideline, which focusses on biologic and tsDMARD treatments. The GWG discussed the appropriateness of initiating a b/tsDMARD first-line, taking into consideration the efficacy, safety and cost effectiveness of conventional synthetic, biologic and tsDMARDS. Based on anecdotal and observational data supporting the efficacy of csDMARDs, especially methotrexate, in achieving low disease activity/remission in PsA and from a cost-effective perspective, the group agreed that a csDMARD should be initiated first-line. There is little evidence to base a judgement on how many csDMARDs should be failed before considering a b/tsDMARD therapy; however, two relevant randomized controlled trials addressing eligibility for b/tsDMARDs were discussed: the SEAM-PsA and the CONTROL studies. The SEAM-PsA trial compared etanercept to etanercept plus methotrexate combination therapy and methotrexate monotherapy. The results demonstrated superiority of etanercept over methotrexate [24]. The CONTROL trial compared dose escalation of methotrexate to the addition of TNFi in people with inadequate disease control PsA after initial methotrexate therapy. A significantly higher proportion of individuals achieved minimal disease activity (MDA) at week 16 after introducing adalimumab compared with dose escalation of methotrexate [25]. The GWG therefore proposed earlier use of a b/tsDMARD therapy after failure of just one csDMARD be considered in those individuals with poor prognostic factors (polyarticular disease, high systemic inflammation levels, presence of radiographic erosions or significantly impaired functional ability) [6, 26–29] or severe active disease.

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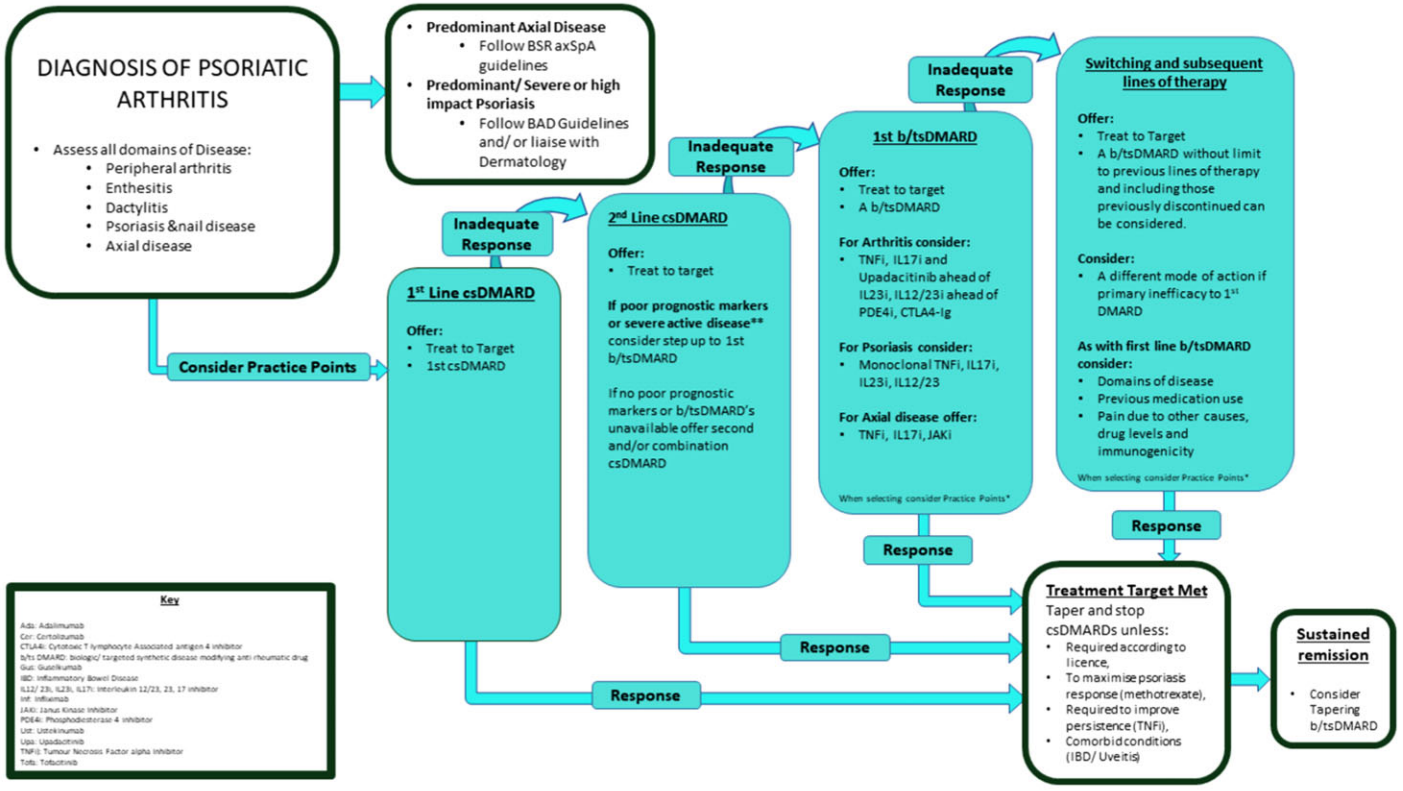
FIG. 1 Summary algorithm for the treatment of an individual with PsA with b/tsDMARDS


DIAGNOSIS OF PSORIATIC ARTHRITIS
Assess all domains of Disease:
Peripheral arthritis
Enthesitis
Dactylitis
Psoriasis &nail disease
Axial disease
Predominant Axial Disease
Follow BSR axSpA guidelines
Predominant/ Severe or high impact Psoriasis
Follow BAD Guidelines and/ or liaise with Dermatology
Consider Practice Points
1st Line csDMARD
Offer:
Treat to Target
1st csDMARD
Inadequate Response
2nd Line csDMARD
Offer:
Treat to target
If poor prognostic markers or severe active disease** consider step up to 1st b/tsDMARD
If no poor prognostic markers or b/tsDMARD's unavailable offer second and/or combination csDMARD
Inadequate Response
1st b/tsDMARD
Offer:
Treat to target
A b/tsDMARD
For Arthritis consider:
TNFi, IL17i and Upadacitinib ahead of IL23i, IL12/23i ahead of PDE4i, CTLA4-Ig
For Psoriasis consider:
Monoclonal TNFi, IL17i, IL23i, IL12/23
For Axial disease offer:
TNFi, IL17i, JAKi
When selecting consider Practice Points*
Inadequate Response
Switching and subsequent lines of therapy
Offer:
Treat to Target
A b/tsDMARD without limit to previous lines of therapy and including those previously discontinued can be considered.
Consider:
A different mode of action if primary inefficacy to 1st DMARD
As with first line b/tsDMARD consider:
Domains of disease
Previous medication use
Pain due to other causes, drug levels and immunogenicity
When selecting consider Practice Points*
Response
Response
Response
Response
Treatment Target Met
Taper and stop csDMARDs unless:
Required according to licence,
To maximise psoriasis response (methotrexate),
Required to improve persistence (TNFi),
Comorbid conditions (IBD/ Uveitis)
Sustained remission
Consider Tapering b/tsDMARD
Key
Ada: Adalimumab
Cer: Certolizumab
CTLA4: Cytotoxic T lymphocyte Associated antigen 4 inhibitor
b/ts DMARD: biologic/ targeted synthetic disease modifying anti rheumatic drug
Gus: Guselkumab
IBD: Inflammatory Bowel Disease
IL12/ 23i, IL23i, IL17i: Interleukin 12/23, 23, 17 inhibitor
Inf: Infliximab
JAKi: Janus Kinase inhibitor
PDE4i: Phosphodiesterase 4 inhibitor
Ust: Ustekinumab
Upa: Upadacitinib
TNFi: Tumour Necrosis Factor alpha inhibitor
Tofa: Tofacitinib

Practice Points*

i)Select b/tsDMARDS typically based on PsA phenotype and comorbidities:
- If moderate/ severe or recurrent uveitis consider Adalimumab or monoclonal TNFi
- If CD offer Ada, Inf, Cer, Ust, Consider Gus.
- If UC Offer Ada, Inf, Gol, Ust, Tofa, Consider Upa.

ii) Concomitant csDMARDS
- Concomitant csDMARDS are not routinely required to improve efficacy (except Tofacitinib).
- Consider concomitant csDMARDS to maximise skin response (methotrexate), improve persistence (with TNFi) or for comorbidity (ie IBD/ Uveitis)

iii) Consider signposting to weight loss and smoking cessation interventions if required to improve drug persistence/ disease activity

iv) Where multiple modes of action are equally clinically appropriate cost of treatment should be taken in to consideration

v) **Defined as at least three tender and three swollen joints or those with fewer joints and either poor prognostic markers or severe disease impact defined as ≥2 domains involved, extraarticular involvement or impaired quality of life

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ii. In people with active peripheral psoriatic arthritis, with inadequate response or intolerance to csDMARDs, offer a bDMARD (TNFi, IL12/23i, IL-17i, IL-23i, CTLA4-Ig) or tsDMARD (JAKi, or PDE4i) (GRADE 1A, 94%). When selecting therapy, consider using TNFi, IL17i or upadacitinib (UPA) ahead of IL12/23i or IL23i ahead of PDE4i ahead of CTLA4-Ig (GRADE 2B, SoA 88%).

A summary of the results from RCTs of (b/ts)DMARDs in PsA is shown in Table 1. The data supporting the first recommendation to offer a b/tsDMARD was based on trials of medication *vs* placebo in the relevant domains of disease. There are no data to support optimal selection of drugs for individuals, but the guideline group developed a consensus recommendation to support biologic choice based on efficacy data, speed of onset and adverse events (Table 1). TNF inhibitors remain the most widely used first line biologic in PsA and none of the other therapies have shown superiority to them for articular disease. Head-to-head studies now exist for IL-17i and upadacitinib showing non-inferiority to TNFi, hence their inclusion as potential first choices. Despite a lack of head-to-head data, there were concerns that clinical responses to IL12/23i, IL23i, PDE4i and CTLA4-Ig might be slightly lower and slower than TNFi. Physicians should be aware of the MHRA safety warning around the use of tofacitinib [30]. The safety data demonstrating increased rates of venous thromboembolic disease (VTE), major cardiovascular event (MACE) and malignancy with tofacitinib compared with TNFi available at the time of writing prompted the committee to differentiate between upadacitinib and tofacitinib in the recommendation.

PsA with enthesitis

iii. In people with active psoriatic enthesitis, with inadequate response or intolerance to a csDMARD, offer any bDMARD (TNFi, IL12/23i, IL-17i, IL-23i) or tsDMARD (JAKi, or PDE4i) (GRADE 1A, SoA 91%).

PsA with dactylitis

iv. In people with active psoriatic dactylitis, with inadequate response or intolerance to a csDMARD, offer any bDMARD (TNFi, IL12/23i, IL-17i, IL-23i) or tsDMARD (JAKi, or PDE4i) (GRADE 1A, SoA 92%).

Active enthesitis and dactylitis are seen in many PsA patients and are usually assessed clinically. Where any question exists as to the cause of pain, additional imaging (ultrasound or magnetic resonance imaging) may be helpful. Positive enthesitis and dactylitis outcomes were seen with all of the medications included in the SLR. Typically, these are as secondary outcomes in peripheral arthritis studies, although there are a small number of specific trials in enthesitis or dactylitis. Some older drugs (Table 1) did not collect these outcomes in the initial phase 3 trials and therefore have poorer quality evidence. However, the group agreed that there was no evidence of differentiation within the drug classes and so all drugs within each class are recommended equally. However, we note that the use of biologics for people with less than three tender or swollen joints is not currently permitted by NICE TAGs, which impede access to therapies for these indications.

PsA with axial disease

v. In people with active psoriatic axial disease, with inadequate response or intolerance to at least two NSAIDs, offer any TNFi or IL-17i or consider a JAKi (GRADE 1A, SoA 92%).

In the literature search, evidence of an improvement in the BASDAI was seen in people with evidence of axial manifestations within the peripheral PsA trials. However, the group noted that the BASDAI is not specific to axial disease and is heavily influenced by disease activity in other domains of PsA. There was one specific axial study in a population with PsA who had physician-reported axial manifestations, and this found evidence of a clinical and imaging benefit for an IL-17Ai (secukinumab) [31]. The group also utilized results from ankylosing spondylitis (AS) and axial spondyloarthritis (aAxSpA) trials to support the recommendations. There are positive trials for TNFi, IL-17i and JAKi in axial SpA. In contrast, there are trials for of an IL-12/23i that were stopped early, a negative trial for apremilast and a negative trial for an IL-23i. The group agreed to a practical approach, utilizing what is known from AS/AxSpA studies to support the evidence found for small subgroups in the PsA trials and the single trial in PsA where all people had axial manifestations. The evidence from the SLR supporting these recommendations can be viewed in supplementary file S1, available at *Rheumatology* online.

PsA with extra-articular manifestations (psoriasis, uveitis, inflammatory bowel disease)

vi. Where a person has associated conditions alongside their psoriatic arthritis, such as psoriasis, uveitis and/or IBD, a multidisciplinary and multispecialty approach should be taken for their care including timely discussions prior to systemic treatment changes. Be aware of other licensed indications and option for differential dosing of common medications in different indications to optimize doses for each individual (GRADE 1B, SoA 98%).

Psoriasis

vii. In the presence of psoriasis, offer concomitant topical therapy (in line with NICE CG 153) (GRADE 1A, SoA 96%).

viii. In the presence of psoriasis and/or nail psoriasis, all currently licensed b/tsDMARDs can be offered but consider prioritizing therapies recommended use for psoriasis: monoclonal TNFi, IL-17i, IL-12/23i or IL-23i summarized in publication [32] (GRADE 1A, SoA 93%).

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Table 1 Summary of key information relating to bDMARDs and tsDMARDS in PsA

	ADA	CZP	ETN	GOL	IFL	ABA	UST	SEC	IXE	GUS	TOFA	UPAD	APR[d]
Year of licence (UK)	2006	2014	2002	2009	2006	2017	2014	2015	2017	2021	2018	2021	2014
Licence in PsA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Phase 3 data in AS/AxSpA	✓	✓	✓	✓	✓	X	✓	✓	✓	X	✓	✓	X
Licence in AS/AxSpA	✓	✓	✓	✓	✓	X	✓	✓	✓	X	X	X	X
Phase 3 data in IBD	✓	✓ (CD)	X	✓ (UC)	✓	X	✓	X	X	✓ (CD)	✓ (UC)	✓ (UC)	X
Licence in IBD	✓	✓[e] (CD)	X	✓ (UC)	✓	X	✓	X	X	X	✓ (UC)	✓[e] (UC)	X
Licence in uveitis	✓	X	X	X	X	X	X	X	X	X	X	X	X
ACR50 at week 12–16 (%)	PBO 3	PBO 12	PBO 4	PBO 2	PBO 2	N/A	N/A	PBO 9	PBO 5	N/A	PBO 10	PBO 13	PBO 7
	ADA 33	CZP 35	ETN 40	GOL 29	IFL 39	N/A	N/A	SEC 40	IXE 34	N/A	TOFA 28	UPAD 38	APR 13
ACR50 at week 24 (%)	PBO 6	PBO 15	PBO 4	PBO 4	PBO 4[c]	PBO 15	PBO 9	PBO 9	PBO 15	PBO 14	N/A	PBO 19	PBO 4
	ADA 40	CZP 42	ETN 37	GOL 35	IFL 41[c]	ABA 25	UST 26	SEC 46	IXE 40	GUS 31	TOFA 38	UPAD 52	APR 20
PASI75 at week 12–16 (%)	PBO 4	PBO 17	N/A	PBO 3	PBO 2	N/A	PBO 9	PBO 13	PBO 8	N/A	PBO 15	PBO 21	PBO 6
	ADA 49	CZP 43	N/A	GOL 49	IFL 65	N/A	UST 50	SEC 65	IXE 75	N/A	TOFA 43	UPAD 63	APR 22
PASI75 at week 24 (%)	PBO 1	PBO 20	PBO 3	PBO 1	PBO 1[c]	PBO 10	PBO 11	PBO 32	PBO 10	PBO 23	N/A	N/A	PBO 5
	ADA 59	CZP 56	ETN 23	GOL 59	IFL 60[c]	ABA 18	UST 60	SEC 72	IXE 71	GUS 79	TOFA 46	N/A	APR 21
Enthesitis efficacy *vs* placebo	N/A	✓	N/A	✓	✓	X	✓	✓	✓ (pooled)	✓ (pooled)	✓ (pooled)	✓	✓ (pooled)
Dactylitis efficacy *vs* placebo	N/A	✓	N/A	✓	✓	X	✓	✓	✓	✓ (pooled)	✓ (pooled)	X	✓ (pooled)
MDA rates at week 24	PBO 6[b]	PBO 6	N/A	PBO 1	N/A	PBO 8[a]	N/A	PBO 15	PBO 15	PBO 11	PBO 19	PBO 12	N/A
	ADA 36[b]	CZP 33	N/A	GOL 28	N/A	ABA 12[a]	N/A	SEC 41	IXE 30	GUS 23	TOFA 26	UPAD 37	N/A
Contraindications	NY class 3/4 heart failure										Severe hepatic impairment	Severe hepatic impairment	
Key safety issues	Demyelination Non-melanoma skin cancer Infections						Exfoliative dermatitis	IBD Fungal infections including candida			Herpes zoster/ VTE/malignancy risk/MACE		Suicidal thought and behaviour

[a]Mixed population with some TNFi exposure. [b]Data on subset with all data available and baseline BSA > 3%. [c]Data at 24 weeks from IMPACT2 study only. [d]Week 12 data based on PALACE 2 and 3, week 24 data based on PALACE 1, all trials mixed population with TNF exposure. [e]Licensed in some countries but not currently in the UK. ABA: abatacept; ACR50: American College of Rheumatology 50% response; ADA: adalimumab; APR: apremilast; AxSpA: axial spondyloarthritis; CD: Crohn's disease; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; GUS: guselkumab; INF: infliximab; IXE: ixekizumab; MDA: minimal disease activity; PASI75: psoriasis area and severity index 75% response; PBO: placebo; SEC: secukinumab; TOFA: tofacitinib; UC: ulcerative colitis; UPAD: upadacitinib; UST: ustekinumab.

ix. In the presence of significant [significant psoriasis is defined as extensive psoriasis (BSA $\geq$ 10 or PASI $\geq$ 10) or localised psoriasis associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites)] psoriasis, be aware that IL-17i and IL23i have superior evidence of efficacy over TNFi (GRADE 1A, SoA 92%).

The studies included in the SLR often reported psoriasis outcomes in people with 3% or more body surface area (BSA) plaque psoriasis. The SLR found a benefit for all of the bDMARDs and tsDMARDS included. In the dermatology literature, there are an increasing number of head-to-head trials comparing bDMARDs in psoriasis with evidence of superior efficacy for IL-17i and IL-23i over TNFi. However, the guideline group agreed that psoriasis tends to be less severe in rheumatology clinics and it is unlikely that such large disparities will exist in this population. Where psoriasis is more severe, then the discussion between the multidisciplinary team is important to select therapy. Further support is available in the clinical implementation toolkit developed by the British Association of Dermatologists.

Uveitis

x. In the presence of a mild relapse of anterior uveitis, follow standard treatment with concomitant topical therapy (GRADE 1A, SoA 94%).
xi. In the presence of moderate to severe sight threatening uveitis or multiple recurrent relapses, consider adalimumab or another monoclonal TNFi (GRADE 1A, SoA 97%).
xii. Refer to the global consensus guideline [33] or NHS England guideline [34] for additional advice on management of uveitis (GRADE 1C, SoA 96%).

There is little evidence for the management of uveitis specifically in people with psoriatic arthritis but there are many trials in wider populations of either people with uveitis or those with uveitis and spondyloarthritis. The guideline group therefore considered evidence from this wider population within existing ophthalmology guidelines and pathways. The evidence from the SLR supporting these recommendations can be viewed in supplementary file S2, available at *Rheumatology* online.

IBD

xiii. In the presence of suspected relapse of IBD, discuss with gastroenterology as a first step (GRADE 1C, SoA 94%).
xiv. In the presence of moderate to severe Crohn's disease, offer any of adalimumab, infliximab, certolizumab, ustekinumab or consider IL-23i (GRADE 1A, SoA 93%).
xv. In the presence of moderate to severe UC, offer any of adalimumab, infliximab, golimumab, ustekinumab or tofacitinib, or consider upadacitinib (GRADE 1A, SoA 93%).
xvi. Prior to prescription of an IL-17i, consider GI referral for people with un-investigated persistent lower GI symptoms or people with a strong family history of IBD (GRADE 2C, SoA 93%).
xvii. Do not use IL-17i in people with active Crohn's disease (GRADE 1B, SoA 88%).
xviii. IBD is not an absolute contraindication to commencement of an IL17i; however, secukinumab and ixekizumab are not recommended in individuals with IBD. Exercise caution and consult gastroenterology team before offering IL-17i to people with controlled UC or Crohn's disease. If used, individuals and their clinicians should be regularly monitoring for symptoms compatible with IBD (GRADE 1C, SoA 89%).

As for uveitis, there was no evidence to support the literature search specific to people with PsA and IBD. This guideline therefore considered evidence for relevant bDMARDs and tsDMARDs in trials of people with IBD to allow rheumatologists to understand their effectiveness. Conditional recommendations are included where recent evidence support efficacy in a phase 3 trial. The evidence for the adverse IBD effects of IL-17i has led to a cautious approach in this guideline. They are not universally excluded but should only be prescribed where other possible options have failed, and the person has well-controlled IBD. Further information is available in guidelines published by the British Society of Gastroenterology [35] and the European Crohn's and Colitis Organisation [36]. The evidence from the SLR supporting these recommendations can be viewed in supplementary file S3, available at *Rheumatology* online.

Treatment strategy

xix. A treat-to-target strategy, whereby an individual's disease activity is proactively measured and treatment escalated accordingly, should be offered to all people with psoriatic arthritis who require treatment (GRADE 1A, SoA 96%).
xx. The treat-to-target strategy should aim for remission or alternatively low disease activity, taking into account patient goals, associated conditions and co-morbidities, and non-inflammatory causes of pain (GRADE 1B, SoA 96%).

The evidence from the TICOPA trial indicated that a treat-to-target strategy was effective across a range of disease domains and this was supported by the group's own experiences. Therefore, a recommendation was made to offer this strategy to people with PsA utilizing regular and validated measurements of disease activity. A second recommendation was made based on consensus in the group that limiting the target to a single measure did not account for the totality of the disease effects. Therefore, the group recommended a disease activity target while also indicating that physicians should consider the patient goals they established early in the

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process, a person's co-morbidities, and other possible causes of pain. Incorporating this approach would keep the person's experiences at the centre of the care. Further advice on treat-to-target in PsA is available in specific international recommendations [16]. The evidence from the SLR supporting these recommendations can be viewed in supplementary file S4, available at *Rheumatology* online.

xxi. In people with psoriatic arthritis who are on treatment and in a stable low disease activity state across disease domains and associated conditions, consider dose reduction or dose spacing of medication following shared decision making with the patient and in consultation with the other specialists involved in their care (GRADE 2B, SoA 98%).

The literature search identified one RCT of treatment withdrawal involving 17 people with PsA and was graded as low quality. However, the clinicians on the guideline group all indicated that they utilized some form of dose tapering in some cases within their usual practice. Given that many bDMARDs and tsDMARDs have standard doses, this is often done by stretching out the interval between doses, e.g. taking adalimumab 40 mg every 3 weeks. Shared decision making is thought to be very important for this process. People should not be forced to taper if they are unwilling as the evidence for a benefit is not strong enough. If considering tapering, there should be meaningful involvement of all the specialists involved in the care of an individual in this decision. The evidence from the SLR supporting these recommendations can be viewed in supplementary file S5, available at *Rheumatology* online.

Prescribing/switching

xxii. When considering treatment with biosimilars for people with PsA, refer to the British Society for Rheumatology 2018 factsheet on biosimilars [37] (GRADE 1C, SoA 96%).

xxiii. In people with active psoriatic arthritis beginning b/tsDMARDs, the routine use of concurrent csDMARDs is not required but concurrent csDMARDs may be required for the drug licence and may be considered to maximize effectiveness for skin disease, IBD or uveitis and/or to improve persistence with TNFi (GRADE 1A, SoA 97%).

xxiv. In people with active psoriatic arthritis, with inadequate response or intolerance to a b/tsDMARD, offer any of the current licensed b/tsDMARD treatments (GRADE 1A, SoA 94%).

xxv. When selecting therapies, following an inadequate response or intolerance to a b/tsDMARD, consider the following (GRADE 2B, SoA 96%):
   a. the domains of disease relevant in that individual, previous medication use, and associated conditions such as psoriasis, uveitis, and IBD, as with first-line b/tsDMARDS;
   b. in people who have primary inefficacy to a b/tsDMARD, consider a different mode of action for the next treatment; and
   c. in people who have developed secondary inefficacy to a b/tsDMARD, consider drugs with the same mode of action first; however, all currently licenced b/tsDMARDS, without limit to previous lines of therapy and including those previously discontinued can be considered.

Large-scale switches to biosimilar medications have occurred and continue to occur as more biosimilar medications become available. These are decisions rooted in finance rather than formal efficacy and there is very little evidence for or against switching. This guideline is utilizing the recommendations held within the 2018 BSR factsheet on biosimilars. It is a consensus document and among its key recommendations it states that people should be offered the most cost-effective biologic medications, encouraging shared decision-making and integration of the wider treatment group in decision-making, and not undertaking sequential switching. The guideline recommends that people can switch back to the originator if they lose efficacy or there are safety issues with the new biosimilar. The evidence from the SLR supporting these recommendations can be viewed in supplementary file S6, available at *Rheumatology* online.

One RCT and two observational studies related to concurrent use of csDMARDs were identified in the literature search. All of these studied TNF inhibitors and indicated that there was no clinically important benefit for the routine use of csDMARDs. However, the group discussed other data outside the SLR particularly related to longevity of medications in national biologics registries. The group also raised the issue of csDMARD use for other indications such as psoriasis or related SpA conditions. The evidence from the SLR supporting these recommendations can be viewed in supplementary file S7, available at *Rheumatology* online.

Lack or loss of response to advanced therapies is a relatively common problem in PsA. While there are an increasing number of trials addressing efficacy of treatments in populations who are TNFi experienced, there is little evidence to guide optimal therapy selection for individuals. There are no studies looking at efficacy in people who have lost response to drugs with other modes of action. Therefore, no specific treatment class recommendations are made. Generally, the guideline group felt that after primary inefficacy to a particular drug, it would not make sense to try another drug from the same class, but an alternative mode of action should usually be selected in the first instance, reserving them for future lines of therapy. In contrast, after secondary inefficacy the same mode of action may be the most effective treatment. However, further studies around treatment sequencing are urgently needed to guide this approach. Pending data to the contrary the committee felt that all licenced b/tsDMARDS, without limit to previous lines of therapy, including those previously discontinued should

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remain available as treatment options. The evidence from the SLR supporting these recommendations can be viewed in supplementary file S8, available at *Rheumatology* online.

Lifestyle choices

xxvi. People with PsA should have their height, weight and BMI recorded (GRADE 2B, 94%). In people with PsA who are overweight or obese, offer weight loss support and signpost to relevant services to maximize response and long-term medication effectiveness of biologics and targeted synthetic DMARDs (GRADE 1A, SoA 98%).

xxvii. In people with PsA, treatment selection should not be affected by a person's weight (GRADE 2C, SoA 88%).

The SLR showed similar efficacy for the medications *vs* placebo, but there were not enough data to differentiate between treatments. Therefore, the group agreed that treatment options for overweight/obese adults with PsA were identical to those offered to the general PsA population. In obese individuals, clinicians should prescribe the appropriate dose for any medication with weight-based dosing (e.g. infliximab, golimumab). It is important to note that people with PsA who are overweight/obese outnumber those of normal weight in the trials reviewed in the literature, so the data contain significant representation from this group. In the SLR, there were no studies addressing weight loss, but the group were aware of additional studies examining the benefits of weight loss in PsA. In both cases they broadly indicated a benefit of weight loss in the population [38, 39]. The group agreed weight loss is an issue that the clinical team should raise with people with PsA where required. This is due to an understanding that being overweight or obese has a negative impact on disease severity and is thought to lessen the efficacy of treatment. It is also known to be linked to more general medical problems such as metabolic syndrome and depression. There is a key role for other specialities and allied health professionals including dieticians, physiotherapists, occupational therapists and podiatrists in supporting interventions around diet and exercise/activity for people who are overweight. The evidence from the SLR supporting these recommendations can be viewed in supplementary files S9 and S10, available at *Rheumatology* online.

xxviii. People with PsA should have their smoking status recorded (GRADE 2B, SoA 97%).

xxix. In people with PsA who are smokers, signpost to smoking cessation support services to maximize treatment response, persistence and improve general health (GRADE 1A, SoA 99%).

xxx. In people with PsA, treatment selection should not be affected by the person's smoking status although doses should be adjusted appropriately (GRADE 2C, SoA 96%).

There was little clinical effectiveness evidence for b/tsDMARDs comparing smokers and non-smokers so no recommendation was made prioritizing any b/tsDMARD treatment over another. For general health benefits, particularly in people with PsA who often have other risk factors for cardiovascular disease, appropriate smoking cessation support was recommended. The evidence from the SLR supporting these recommendations can be viewed in supplementary files S11 and S12, available at *Rheumatology* online.

Applicability and utility

This guideline represents a framework to support clinicians prescribing bDMARDs and tsDMARDs for psoriatic arthritis. As in all guidelines, we recognize that individual patient circumstances will have an important influence on clinical decision-making and clinicians should continue to implement shared care approaches alongside their patients. Failure to adhere to this guideline should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence.

As in other BSR guidelines, we recommend that biologic or tsDMARD initiation should only take place under the supervision of a rheumatologist. This guideline does make recommendations on widening access to bDMARDs and tsDMARDs beyond the scope of current NICE TAGs. We recognise that currently this may not be possible to implement, but believe that our recommendations are evidence-based.

Audit tool

A model audit tool is available via the BSR website and in supplementary material S13, available at *Rheumatology* online.

Summary and conclusions

Since 2012, there has been a rapid expansion in the advanced therapies licensed for the treatment of PsA. While this is clearly of benefit to people with PsA, it does bring additional challenges for clinicians in selecting the best therapy for individuals. This guideline aims to provide practical support to rheumatology clinicians to support the prescription of bDMARDs and tsDMARDs in PsA.

Acknowledgements

We gratefully acknowledge the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the members of their Treatment Recommendations working group who shared extracted data on treatment RCTs for this project.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript. Expenses for travel were paid by the British Society for Rheumatology.

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Disclosure statement: L.C.C. has received honoraria for consultation and educational talks from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Galapagos, Gilead, GSK, Janssen, Eli Lilly, Medac, Moonlake, Novartis, Pfizer and UCB. L.C.C. is also actively involved in studies evaluating new drugs for PsA; these were only included in the guideline if identified in the systematic literature review. W.T. has received research grant income from Eli Lilly and Janssen, as well as consultancy fees, speaker fees or financial support to attend conferences from Amgen, Eli Lilly, Janssen, Novartis, UCB. D.C. is the Chief Executive of Psoriasis and Psoriatic Arthritis Alliance. A.D. has acted as a consultant for Janssen, Novartis, Roche and AbbVie. A.D. is also the Director of the UCL Institute of Ophthalmology and has received funding from NIHR to start a trial on adalimumab in uveitis. A.F. has received educational support to attend conferences from or acted as a consultant or speaker for AbbVie, Almirall, Celgene, Eli Lilly, Leo Pharma, Novartis, Pfizer, Janssen and UCB. N.G. has participated in advisory boards for AbbVie, Eli Lilly, Janssen, Novartis and UCB, and is a trustee of British Psoriatic Arthritis Consortium Clinical Trials, working with Abbvie, Eli Lilly, Gilead and Novartis. P.H. has received grants and research support from Novartis, and honoraria or consultation fees from Pfizer, Eli Lilly, Janssen and Celgene. D.J. has acted as a Principal/Chief Investigator on industry-sponsored clinical trials, and has received research, development and/or education grants from Pfizer, AbbVie, Eli Lilly, Biogen, GSK, Celgene, Novartis, Gilead, UCB, Janssen, Celltrion and Sandoz. Education grants have been paid to Spondyloarthritis Training and Education (SPATE) UK Ltd, of which D.J. is a Co-Director. D.J. has received speaker fees for advisory boards/consultancy fees from Novartis, Eli Lilly, Gilead, Biogen, UCB, Janssen, AbbVie, Roche, Pfizer and Sandoz. D.J. is also a trustee to Cambridge Arthritis Research Endeavour (CARE) and British Psoriatic Arthritis Consortium (Brit-PACT), as well as a Research Steering Committee member for GRAPPA and a member of the Association for Assessment of Axial Spondyloarthritis (ASAS). G.J. is Chief Investigator of the British Society for Rheumatology Psoriatic Arthritis Register, for which the University of Aberdeen has received research grants from the British Society for Rheumatology and, in turn, Amgen. The University of Aberdeen has also received grant income from GSK for a project on which G.J. is a co-investigator. S.K. has received honoraria from Novartis and Celltrium. T.R. has received speaker or consultancy fees from AbbVie, Janssen, Novartis and UCB, as well as research grants from AbbVie, Amgen, BMS, Boehringer-Ingelheim, GSK, Janssen, Lilly, Novartis and UCB. T.R. is a trustee and executive steering group member for Brit-PACT and BRITSpA and is Chair of the Versus Arthritis Adult Inflammatory Arthritis Research Advisory Group. C.S. is GSTT-PI/co-investigator on clinical trial work or studies sponsored or supported by AbbVie, GSK, Janssen, Novartis, Pfizer, Regeneron, Roche, Boehringer Ingleheim, NIHR and SOBI. C.S. also works on PSORT and BIOMAP, which have multiple industry partners including: AbbVie, Sanquin, Qiagen, Pfizer, Novartis, MedImmune, Janssen, Celgene, Sanofi, LEO Pharma, Boehringer Ingleheim and UBC (list not exhaustive as partners change, please see psort.org and https://www.biomap-imi.eu/ for current information). C.S. is also a NICE expert advisor on interventions in psoriasis and eczema for STAs; Chair and committee member for multiple guidelines from the British Association of Dermatologists; member of the International Psoriasis Council. L.C.C. is an NIHR Clinician Scientist funded by a National Institute for Health Research Clinician Scientist award. The work was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The remaining authors have declared no conflicts of interest.

Data availability statement

All relevant data produced during the guideline development process are presented in this manuscript or in the accompanying supplementary material.

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Systemic Lupus Erythematosus

FAIK NOORI

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Arthritis & Rheumatology
Vol. 71, No. 9, September 2019, pp 1400–1412
DOI 10.1002/art.40930
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SPECIAL ARTICLE

2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus

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This criteria set has been approved by the European League Against Rheumatism (EULAR) Executive Committee and the American College of Rheumatology (ACR) Board of Directors. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All EULAR/ACR-approved criteria sets are expected to undergo intermittent updates.

The ACR is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.

Objective. To develop new classification criteria for systemic lupus erythematosus (SLE) jointly supported by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR).

Methods. This international initiative had four phases. 1) Evaluation of antinuclear antibody (ANA) as an entry criterion through systematic review and meta-regression of the literature and criteria generation through an international Delphi exercise, an early patient cohort, and a patient survey. 2) Criteria reduction by Delphi and nominal group technique exercises. 3) Criteria definition and weighting based on criterion performance and on results of a multi-criteria decision analysis. 4) Refinement of weights and threshold scores in a new derivation cohort of 1,001 subjects and validation compared with previous criteria in a new validation cohort of 1,270 subjects.

Results. The 2019 EULAR/ACR classification criteria for SLE include positive ANA at least once as obligatory entry criterion; followed by additive weighted criteria grouped in 7 clinical (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and 3 immunologic (antiphospholipid antibodies, complement proteins, SLE-specific antibodies) domains, and weighted from 2 to 10. Patients accumulating ≥10 points are classified. In the validation cohort, the new criteria had a sensitivity of 96.1% and specificity of 93.4%, compared with 82.8% sensitivity and 93.4% specificity of the ACR 1997 and 96.7% sensitivity and 83.7% specificity of the Systemic Lupus International Collaborating Clinics 2012 criteria.

Conclusion. These new classification criteria were developed using rigorous methodology with multidisciplinary and international input, and have excellent sensitivity and specificity. Use of ANA entry criterion, hierarchically clustered, and weighted criteria reflects current thinking about SLE and provides an improved foundation for SLE research.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with variable clinical features (1,2). SLE manifestations are associated with multiple autoantibodies, ensuing immune complex formation and deposition, and other immune processes (2,3). This complex clinical presentation and pathogenesis makes SLE a difficult disease to grasp and define. Classification criteria are essential for the identification of relatively homogeneous groups of patients for inclusion in research studies and trials (4,5). The 1982 revised American College of Rheumatology (ACR) SLE classification criteria (6) and their 1997 revision (7) have been used worldwide. Since then, our understanding of the disease has advanced. Additional specific skin manifestations were described, some clinical symptoms were better understood, and immunologic tests, such as diminished levels of serum complement components C3 and C4 or testing for anti–β_2-glycoprotein I antibodies, entered routine clinical practice. Better understanding of organ system involvement, such as mucocutaneous abnormalities, led to questions about whether some of the independently counted criteria were in fact manifestations of the same phenomenon (8).

The 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria addressed many of these issues (9). Mucocutaneous and neuropsychiatric manifestations were added, as were hypocomplementemia and new antiphospholipid antibody tests; and criteria definitions were refined. The SLICC criteria emphasized that SLE is primarily an autoantibody disease, requiring at least one immunologic criterion to be present, and

A video abstract of this article can be found at https://drive.google.com/open?id=1Ck_aksrVF9HhuHvI9k9komaKgjPmsuyK.

This article is published simultaneously in the September 2019 issue of *Annals of the Rheumatic Diseases.*

Supported by the European League Against Rheumatism and the American College of Rheumatology. One part of the derivation and validation cohort was supported by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH.

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No potential conflicts of interest relevant to this article were reported.

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Submitted for publication November 25, 2018; accepted in revised form May 1, 2019.

categorized histology-proven nephritis compatible with SLE as sufficient for classification, if antinuclear antibodies (ANAs) or antibodies to double-stranded DNA (dsDNA) were present. While achieving their goal of increasing sensitivity, the SLICC criteria have lower specificity than the 1997 ACR criteria (9,10).

Existing SLE classification criteria perform better in patients with longstanding disease than in new-onset SLE (11), and there is an increasing recognition and demand that subjects with early SLE should be included in clinical studies and trials. We therefore attempted to enrich our sample populations for early SLE in several phases of the project.

In parallel with improved understanding of SLE, the field of classification criteria development has also seen advances (4,12–14). In order to minimize investigator bias, it is now recommended that the cohorts in which the criteria are tested are from independent centers (4). Other methodologic recommendations include a balanced use of both expert-based and data-driven methods, and inclusion of the patient perspective (13,14). The approach chosen for these 2019 European League Against Rheumatism (EULAR)/ACR SLE classification criteria was specifically designed to maintain this balance and to uphold rigorous methodology.

METHODS

Methodologic overview. Using a methodologic approach based on measurement science the criteria were developed in four phases (10): 1) criteria generation, 2) criteria reduction, 3) criteria definition and weighting, and 4) refinement and validation (Figure 1). The whole initiative was overseen by a 12-member steering committee (MA, KHC, DID, MM, RR-G, JSS, DW, DTB, DLK, DJ, TD, and SRJ) nominated by EULAR and the ACR in equal numbers, based on SLE and/or methodologic experience and previous involvement in international projects.

The current project, jointly supported by the EULAR and the ACR, was originally based on two key concepts. One, we hypothesized that the presence of ANA would be better employed as an entry criterion than as a classification criterion (10). Such an approach was thought to reflect underlying SLE pathogenesis, and take into account ANA test characteristics of high sensitivity and limited specificity. Two, we expected individual criteria would not be of equal utility (weight) for the classification of SLE (15), for example, mucosal ulcers versus biopsy-proven lupus nephritis. Accordingly, the validity of using positive ANA as an entry criterion was explicitly addressed in phase I of the current activity (16). Likewise, methodologic strategies to develop weighted criteria were used.

Phase I: Criteria generation. The purpose of phase I was to test ANA as a potential entry criterion and identify candidate criteria that should be considered for SLE classification using both data-based and expert-based methods, including the patient perspective. *Phase Ia* comprised a systematic literature review of Medline, Embase, and the Cochrane databases with meta-regression to evaluate the operating characteristics of ANA testing for consideration as an entry criterion (16). *Phase Ib* consisted of a Delphi exercise of international SLE experts from the Americas, Europe, and Asia (17). These experts included

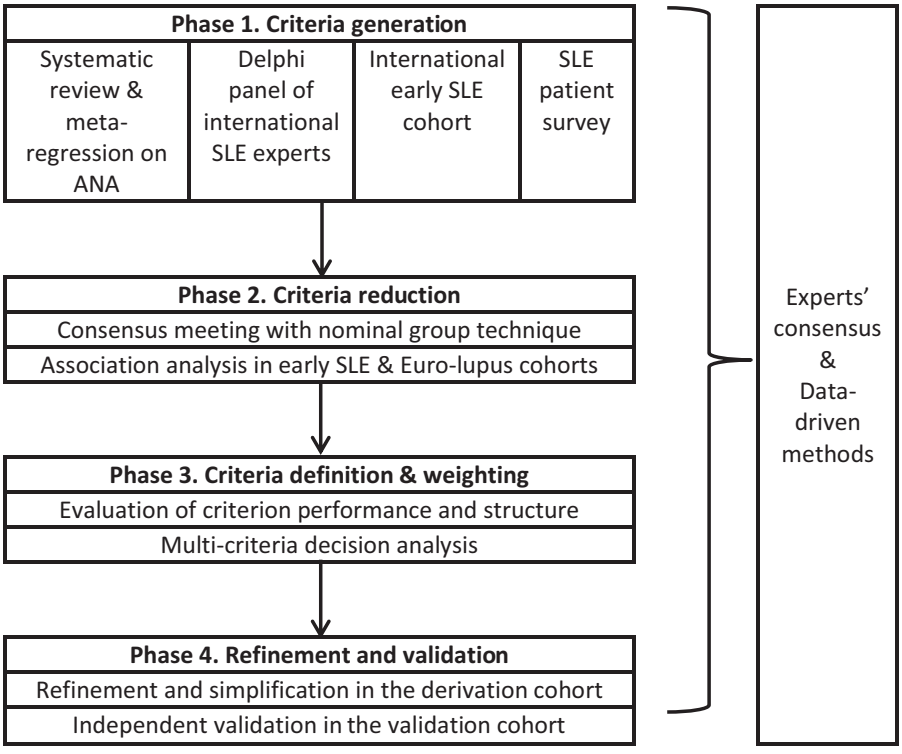
Phase 1. Criteria generation
Systematic review & meta-regression on ANA
Delphi panel of international SLE experts
International early SLE cohort
SLE patient survey
Phase 2. Criteria reduction
Consensus meeting with nominal group technique
Association analysis in early SLE & Euro-lupus cohorts
Phase 3. Criteria definition & weighting
Evaluation of criterion performance and structure
Multi-criteria decision analysis
Phase 4. Refinement and validation
Refinement and simplification in the derivation cohort
Independent validation in the validation cohort
Experts' consensus & Data-driven methods

Figure 1. Development and validation of systemic lupus erythematosus (SLE) classification criteria. ANA = antinuclear antibody.

rheumatologists, dermatologists, nephrologists, pediatricians, and non-clinical SLE researchers, providing a broad perspective. The Delphi participants were asked to nominate a broad set of items potentially useful in the classification of SLE (17). In rounds 2 and 3, participants rated the items from 1 (not at all appropriate) to 9 (completely appropriate) for classification of SLE. Criteria were retained if they reached a median rating of ≥6.5; that is, at least 50% of the ratings in the high range (7, 8, or 9). Participants were also asked about the importance of ANA and histopathology for classification of SLE. *Phase Ic* established an international cohort of patients with early SLE or conditions mimicking SLE to identify criteria that may discriminate subjects with early (less than 12 months) disease (18). *Phase Id* comprised a cross-sectional survey of SLE patients, administered via the quarterly journal of the German SLE patient organization, which asked about symptoms within 1 year before and after the patient's diagnosis of SLE (19). While at a risk of recall bias and not necessarily representative of other regions worldwide, this survey was done to explicitly take a patient standpoint into account.

For phases II and III, additional renowned European and North American SLE experts were nominated by the steering committee and invited to participate.

Phase II: Criteria reduction. *Phase IIa.* The objective of this phase was to select a set of criteria from phase I that maximized the likelihood of accurate classification of SLE, particularly of early disease. An independent panel of seven of the international SLE experts (RC, NC-C, DDG, BHH, FH, EM, and JS-G) ranked the candidate criteria from phase I. A consensus meeting of 19 international SLE experts (n = 7 nominal group technique [NGT] experts + steering committee + DK [moderator]) using NGT was conducted to reduce the list of criteria (20). Data for each candidate criterion were reviewed and discussed until consensus was achieved. The NGT experts voted on items to be retained.

Phase IIb. NGT participants pointed out that some criteria could be correlated. With the idea of potentially clustering criteria into domains, associations between candidate criteria were evaluated separately in two cohorts, the phase Ic early SLE and the Euro-lupus cohorts (21).

Phase III: Criteria definition and weighting. *Phase IIIa.* The operating characteristics of the retained candidate criteria were evaluated by literature review. Candidate criteria were hierarchically organized into clinical and immunologic domains, and definitions for the candidate criteria were iteratively refined. SLE patient advocates participated in the review of data and the steering committee discussions (22).

Phase IIIb. One hundred sixty-four case vignettes reflecting broad SLE clinical presentation were sampled from SLE centers across several countries. A panel of six of the international experts not involved in earlier phases of the project (BD, SJ, WJM, GR-I, MS, and MBU) and 11 members of the steering committee assessed and ranked a representative sample of the cases. Subsequently, at a face-to-face meeting, this panel of 17 international SLE experts iteratively compared pairs of criteria, using multicriteria decision analysis facilitated by 1000Minds software (23). The panel unanimously agreed to further reduce the list of criteria. Based on the results, provisional criteria weights were assigned and a provisional threshold score for classification was determined as the lowest score at which the expert panel had achieved consensus on classifying a case vignette as SLE (24).

Phase IV: Refinement and validation. International SLE experts not involved in phase II or phase III panels were asked to contribute cases diagnosed as SLE and controls with conditions mimicking SLE sampled from patients evaluated at their centers. Each center was asked to contribute up to 100 cases and an equal number of controls, preferentially sampling those with early disease, and regardless of their specific clinical or immunologic manifestations. Pseudonymized data on the criteria were collected using a standardized data collection form. Ethics committee approval and informed consent were obtained as per local requirements. The status ("SLE" or not) of each case underwent independent adjudication by three of four SLE experts (GB, BFH, NL, and CT) from different centers. Queries were sent back to the submitting investigator for clarification. Of this cohort, 501 SLE and 500 control subjects were randomly selected to comprise the derivation cohort, while the remaining 696 SLE and 574 control subjects formed the validation cohort.

Refinement. The performance of the draft criteria set was iteratively tested in the derivation cohort. A data-driven threshold for classification was determined by receiver operating characteristics (ROC) analysis and compared with the provisional expert-based consensus threshold. The data of SLE subjects below the threshold (misclassified) were reviewed for groups of patients with unequivocal SLE who still missed classification, and criteria weights adjusted slightly, while preserving the weighting hierarchy (details below in Results, Phase IV section). Sensitivity and specificity were tested against the ACR 1997 and the SLICC 2012 criteria. In addition, ANA as an entry criterion was tested against not having an entry criterion. Finally, the criteria weights were simplified to whole numbers. Refinements to the criteria set were presented to the steering committee and phase III expert panel, and unanimously endorsed.

Validation. The sensitivity and specificity of the final criteria were tested in the validation cohort and compared with previous SLE criteria sets.

Statistical analysis. Descriptive statistics were used to summarize the data. Confidence intervals (CIs) were calculated using the bias-corrected and accelerated bootstrap method (BCa

method) with B = 2000 bootstrap samples. The BCa method resamples the input data B times (with replacement) and calculates the required statistics (sensitivity, specificity, AUC). Based on the B bootstraps samples, the bias-correction is applied and the associated 95% CIs for the statistics are estimated. The BCa method has proven to yield very accurate coverage of estimated CIs (25). The number B of bootstrap resamples is recommended to be at least B = 1,000. We have chosen B = 2,000 and additionally checked if B = 5,000 bootstraps changed the estimated confidence bounds, which was not the case. Statistical analyses were performed using R, v.3.4.0 (The R Foundation of Statistical Computing).

RESULTS

Phase I: Criteria generation. *Phase Ia: ANA as an entry criterion.* A systematic review of Medline, Embase, and the Cochrane database identified 13,080 patients from 64 studies reporting ANA by immunofluorescence on HEp-2 cells. Meta-regression of the operating characteristics of ANA found a sensitivity of 97.8% (95% CI 96.8–98.5%) for ANA of ≥1:80, supporting use of ANA as an entry criterion (16). Since some SLE centers do not have access to HEp-2 ANA, and in view of ongoing work on the standardization of serology and potential future advances in the field, the steering committee and additional autoantibody consultants (MJF and PLM) recommended the provision "or an equivalent positive ANA test. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended."

Phase Ib: Delphi exercise. One hundred forty-seven international SLE experts nominated 145 candidate criteria (17). By rating the appropriateness for SLE classification, the participants in the second and third Delphi rounds reduced the list to 40 candidate criteria (Supplementary Table 1, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40930/abstract).

Phase Ic: International early SLE cohort. The cohort comprised 616 subjects who had been referred for possible SLE with a disease duration of less than 1 year (n = 389 early SLE and n = 227 mimicking diseases) from North America, Europe, Asia, and South America (18). In addition to supporting many of the 40 candidate criteria derived from the Delphi exercise, the comparison between early SLE and non-SLE patients showed that fever occurred more frequently (34.5% versus 13.7%; $P < 0.001$) in SLE, while SLE patients less commonly suffered from arthralgias (20.3% versus 42.7%; $P = 0.001$) and fatigue (28.3% versus 37%; $P = 0.02$).

Phase Id: Patient survey. Three hundred thirty-nine SLE patients (>99% Caucasian, 93% female) responded to the survey (19). More than half of these patients reported mucocutaneous findings in the first year of their disease (Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.40930/abstract), but also fatigue (89%), joint pain (87%), and fever (54%) (19). Given that these items were highlighted both in the early SLE cohort and the patient survey, fever, fatigue, and arthralgias were forwarded to the next phase in addition to the 40 Delphi items. Accordingly, phases Ia–Id resulted in a total of 43 candidate criteria for consideration (Supplementary Table 1).

Phase II: Criteria reduction. *Phase IIa.* The expert panel NGT exercise reduced the candidate criteria from 43 to 21 (26). The panel distinguished potential "entry criteria," which would be required for classification, from potential "additive criteria." They endorsed "positive ANA (≥1:80 by HEp-2 immunofluorescence)" as an entry criterion. The 20 remaining additive criteria included: lupus nephritis by renal biopsy, autoantibodies, cytopenias, fever, arthritis, serositis, mucocutaneous and neuropsychiatric manifestations (Supplementary Table 1).

Phase IIb. Associations between the candidate criteria were evaluated in 389 subjects in the early SLE cohort and the 1,000 SLE subjects of the Euro-lupus cohort. Modest statistically significant correlations were limited to the mucocutaneous (r = 0.22–0.30), neurologic (r = 0.22), and immunologic (r = 0.33) domains in the early SLE cohort, and this modest correlation was replicated in the Euro-lupus cohort (21). Given these associations, criteria were clustered within domains, so that only 1 criterion within each domain would be counted.

Phase III: Criteria definition and weighting. *Phase IIIa.* Based on the literature, definitions of the 20 candidate additive criteria were refined, using a data-driven evaluation of operating characteristics (22), retaining only feasible items with a prevalence of at least 1% according to literature. Literature review led to the consensus decision to evaluate 5 different candidate criteria within the neuropsychiatric domain (delirium, psychosis, seizure, mononeuropathy, cranial neuropathy) and potential separation of acute pericarditis from pleural or pericardial effusions and between diminished C3 or C4 versus diminished C3 and C4. The resulting 23 candidate criteria (Supplementary Table 1, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40930/abstract) were organized into 7 clinical and 3 immunologic domains, with hierarchical clustering (22). Only the highest-ranking item in each domain was to be counted. Instead of devising exclusion definitions for each criterion, the decision was made to attribute any item to SLE only if no more likely explanation was present. For leukopenia and joint involvement, it was decided to formally test alternative definitions in the derivation cohort. Given the importance of testing for antibodies, particularly for anti-dsDNA, for which tests of relatively low specificity are in use, great care was taken to precisely define testing (Table 1).

Table 1. Definitions of SLE classification criteria*

Criteria	Definition
Antinuclear antibodies (ANA)	ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended
Fever	Temperature >38.3°C
Leukopenia	White blood cell count <4,000/mm³
Thrombocytopenia	Platelet count <100,000/mm³
Autoimmune hemolysis	Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH, AND positive Coombs' (direct antiglobulin) test
Delirium	Characterized by 1) change in consciousness or level of arousal with reduced ability to focus, 2) symptom development over hours to <2 days, 3) symptom fluctuation throughout the day, 4) either 4a) acute/subacute change in cognition (e.g., memory deficit or disorientation), or 4b) change in behavior, mood, or affect (e.g., restlessness, reversal of sleep/wake cycle)
Psychosis	Characterized by 1) delusions and/or hallucinations without insight and 2) absence of delirium
Seizure	Primary generalized seizure or partial/focal seizure
Non-scarring alopecia	Non-scarring alopecia observed by a clinician†
Oral ulcers	Oral ulcers observed by a clinician†
Subacute cutaneous OR discoid lupus	Subacute cutaneous lupus erythematosus observed by a clinician:† Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted). OR Discoid lupus erythematosus observed by a clinician:† Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging (scalp), leading to scarring alopecia on the scalp If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular and/or periappendageal lymphohistiocytic infiltrate. In the scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition may be noted)
Acute cutaneous lupus	Malar rash or generalized maculopapular rash observed by a clinician† If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Perivascular neutrophilic infiltrate may be present early in the course)
Pleural or pericardial effusion	Imaging evidence (such as ultrasound, x-ray, CT scan, MRI) of pleural or pericardial effusion, or both
Acute pericarditis	≥2 of 1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), 2) pericardial rub, 3) EKG with new widespread ST elevation or PR depression, 4) new or worsened pericardial effusion on imaging (such as ultrasound, x-ray, CT scan, MRI)
Joint involvement	EITHER 1) synovitis involving 2 or more joints characterized by swelling or effusion OR 2) tenderness in 2 or more joints and at least 30 minutes of morning stiffness
Proteinuria >0.5 g/24 hours	Proteinuria >0.5 g/24 hours by 24-hour urine or equivalent spot urine protein-to-creatinine ratio
Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class II: Mesangial proliferative lupus nephritis: purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy Class V: Membranous lupus nephritis: global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations

(Continued)

Table 1. *(Cont'd)*

Criteria	Definition
Class III or IV lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class III: Focal lupus nephritis: active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations Class IV: Diffuse lupus nephritis: active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Positive antiphospholipid antibodies	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 APL, GPL, or MPL, or >the 99th percentile) or positive anti-β_2GPI antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant
Low C3 OR low C4	C3 OR C4 below the lower limit of normal
Low C3 AND low C4	Both C3 AND C4 below their lower limits of normal
Anti-dsDNA antibodies OR anti-Sm antibodies	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥90% specificity for SLE against relevant disease controls OR anti-Sm antibodies

* SLE = systemic lupus erythematosus; LDH = lactate dehydrogenase; CT = computed tomography; MRI = magnetic resonance imaging; EKG = electrocardiography; ISN = International Society of Nephrology; RPS = Renal Pathology Society; anti-β_2GPI = anti–β_2-glycoprotein I; anti-dsDNA = anti–double-stranded DNA.
† This may include physical examination or review of a photograph.

Phase IIIb. The 1.5-day in-person consensus meeting using multicriteria decision analysis involved 74 decisions between pairs of criteria. Criteria weights were calculated by 1000Minds software based on these decisions (Table 2). International Society of Nephrology/Renal Pathology Society class III or IV nephritis consistently attained higher weight than class II or V nephritis, so lupus nephritis by histology was separated into 2 different criteria. Class VI lupus nephritis as an end-stage manifestation was unanimously eliminated. Likewise, the experts unanimously voted to not retain mononeuropathy and cranial neuropathy, which had been included into the set of potential neuropsychiatric items in phase IIIa but turned out to add little to SLE classification. The use of weighted criteria led to a sum score that is a measure of the relative probability of a subject having SLE, with higher scores indicating higher likelihood. Experts reached full consensus on a classification of SLE at a provisional threshold score of >83 of a theoretical maximum of 305 (24).

Phase IV: Refinement and validation. Twenty-one centers from the US, Canada, Mexico, Austria, Croatia, France, Germany, Greece, Hungary, Italy, Portugal, Spain, the UK, Turkey, Hong Kong, and Japan submitted a total of 2,339 cases from their cohorts; 1,197 SLE and 1,074 non-SLE diagnoses (Table 3) were verified by 3 adjudicators blinded to the proposed classification criteria system. Due to lack of consensus during adjudication, 68 subjects (2.9%) were excluded from the analysis.

Derivation cohort. Of the 2,271 triple-adjudicated cases, 501 SLE and 500 non-SLE cases were randomly assigned to the derivation cohort. The provisional weighting system derived from phase III was tested in the derivation cohort. ROC analysis suggested a data-driven threshold of ≥70 (of a maximum of 305), with a sensitivity of 95.4% and a specificity of 95.2%, which was superior to the consensus-derived provisional threshold of >83 that had high specificity (98.8%), but lower sensitivity (81.6%). Review of subjects below the threshold of 70 identified a subgroup of SLE subjects with joint involvement and/or leukopenia. Thus, weights for leukopenia and joint involvement were each adjusted (Table 2) to reduce misclassification. When alternative definitions for leukopenia and joint involvement were tested, leukopenia defined as a white blood cell count (WBC) <4000/mm^3 at least once (9) also had a slightly higher sensitivity + specificity (1.944 versus 1.942) than leukopenia defined as WBC <4,000/mm^3 on 2 or more occasions (6,26). Joint involvement defined as EITHER "synovitis involving 2 or more joints, characterized by swelling or effusion," OR "tenderness in 2 or more joints and at least 30 minutes of morning stiffness" (9) had a higher combined sensitivity and specificity than arthritis defined simply as synovitis of 2 or more joints (1.944 versus 1.900). When retested, the revised criteria had increased sensitivity, and maintained sensitivity + specificity. Evaluating ANA as an entry criterion, the criteria with the ANA entry criterion had better performance than without (sensitivity + specificity 1.944 versus 1.930). Next, the weights were simplified by division to whole numbers to achieve a threshold of 10 (Table 2). In the derivation cohort, the sensitivity and specificity of the final criteria set (Figure 2) were reaching the performance benchmarks set for this project (Table 4).

Validation. The validation cohort, that is, the full cohort minus the derivation cohort, comprised 1,270 triple-adjudicated subjects (n = 696 SLE, n = 574 controls). The criteria, with

Table 2. Relative weights of the additive classification criteria items*

Domain	Item	Original	Modification	Revised	Simplified
Constitutional	Fever	13		13	2
Hematologic	Leukopenia	12	+7	19	3
	Thrombocytopenia	26		26	4
	Autoimmune hemolysis	28		28	4
Neuropsychiatric	Delirium	12		12	2
	Psychosis	20		20	3
	Seizure	34		34	5
Mucocutaneous	Alopecia	13		13	2
	Oral ulcers	14		14	2
	SCLE/DLE	29		29	4
	ACLE	38		38	6
Serosal	Effusion	34		34	5
	Acute pericarditis	38		38	6
Musculoskeletal	Joint involvement	34	+4	38	6
Renal	Proteinuria	27		27	4
	Class II/V	55		55	8
	Class III/IV	74		74	10
Antiphospholipid antibodies	Antiphospholipid	13		13	2
Complements	C3 or C4 low	19		19	3
	C3 and C4 low	27		27	4
SLE-specific antibodies	Anti-Sm	40		40	6
	Anti-dsDNA	38		38	6

* Weights derived from the phase III consensus meeting with multicriteria decisions analysis (original), added points for leukopenia and joint involvement (modification), the resulting weights (revised), and the final simplified weights (simplified). SCLE = subacute cutaneous lupus erythematosus; DLE = discoid lupus erythematosus; ACLE = acute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus; anti-dsDNA = anti–double-stranded DNA.

positive ANA as an entry criterion, weighted criteria in 7 clinical domains (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and 3 immunologic domains (antiphospholipid antibodies, low complements, anti-Sm and anti-dsDNA as SLE-specific antibodies), and a classification threshold score of ≥10 (out of a theoretical maximum of 51) (Figure 2), had a sensitivity of 96.1% and a specificity of 93.4% (Table 4). It demonstrated improved performance compared with the ACR 1997 and SLICC 2012 criteria.

DISCUSSION

New SLE classification criteria were developed with support by both the ACR and EULAR. Through a four-phase, iterative process, we have defined an additive, weighted multicriteria system that produces a measure of the relative probability that an individual can be classified as SLE. The system defines a threshold above which experts would classify cases as SLE for the purpose of research studies. We have carefully defined the criteria to improve reliability and precision, and have grouped the criteria into 10 hierarchical domains. We have validated the criteria against a large number of cases, including many patients with manifestations that resemble SLE but who do not have SLE. This approach, as well as the resulting criteria system, represents a paradigm shift for the classification of SLE.

We have defined positive ANA at any time as required entry criterion. There were three possible ways to deal with ANA testing. The previous criteria sets have treated ANA the same as the much more specific antibodies against Sm and dsDNA, which we considered suboptimal given important differences in sensitivity and specificity. We could have excluded ANA completely in classifying lupus, but we still consider ANA a useful test and concept. We therefore decided to test ANA as an entry criterion, which reflects the use of ANA as a highly sensitive screening test.

Criteria using ANA as entry criterion had better performance. During the phase I Delphi exercise, 58% of SLE experts did not feel comfortable and an additional 19% were uncertain about classifying a patient with SLE in the absence of ever having a

Table 3. Demographic characteristics of the derivation and validation cohorts*

	Derivation cohort		Validation cohort	
	SLE	Non-SLE	SLE	Non-SLE
n	501	500	696	574
Female/male	447/54	421/79	608/88	490/84
Age, mean ± SD years	45 ± 14	54 ± 16	45 ± 14	56 ± 16
Disease duration, mean ± SD years	11 ± 8	9 ± 8	11 ± 8	9 ± 8
Ethnicity				
Black	29	10	56	12
East Asian	36	29	53	34
Hispanic	59	48	73	51
South/Southeast Asian	16	6	21	11
White	355	404	480	461
Other	6	3	13	5
SLE	501		696	
Non-SLE		500		574
Adult-onset Still's disease		2		11
Autoimmune thyroiditis		6		5
Behçet's disease		7		9
Cancer		2		3
Inflammatory myositis		37		27
Fibromyalgia		6		3
Membranous nephritis		11		14
Mixed connective tissue disease		9		15
Osteoarthritis		2		0
Primary antiphospholipid antibody syndrome		45		48
Psoriatic arthritis		12		9
Rheumatoid arthritis		94		110
Sarcoidosis		2		2
Sjögren's syndrome		112		124
Spondyloarthritis		5		5
Systemic sclerosis		99		120
Tuberculosis		0		2
Undifferentiated connective tissue disease		16		20
Vasculitis		9		13
Viral infection		5		5
Other		19		29

* Inflammatory myositis includes dermatomyositis, polymyositis, and juvenile dermatomyositis. SLE = systemic lupus erythematosus.

positive ANA (17). The systematic literature review and meta-regression of data on 13,080 subjects demonstrated ANA ≥1:80 to have a sensitivity of 98% with a lower limit of the 95% CI at 97% (16). In the phase I early SLE cohort, 99.5% of the 389 SLE patients were ANA positive (18). The frequencies of ANA-positive SLE patients in the derivation and validation cohorts (99.6% and 99.3%, respectively) were in the same range. Since both in the early SLE cohort and in the derivation and validation cohorts, patients were included in many centers worldwide independent of ANA positivity, the latter data provide additional support for ANA as an entry criterion.

Using ANA as entry criterion means the new criteria cannot classify SLE among patients who are persistently ANA negative. While possibly also distinguished by lower cytokine levels (27) and lower efficacy of immunomodulatory treatment (28), such a subgroup of patients exists. Although small, it may vary in size

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Figure 2. Classification criteria for systemic lupus erythematosus (SLE). § = additional criteria within the same domain will not be counted; * = in an assay with 90% specificity against relevant disease controls. Anti-β_2GPI = anti–β_2-glycoprotein I; anti-dsDNA = anti–double-stranded DNA.

in different populations (16). This patient subset needs to be put high on the scientific agenda for further investigation. Additional characterization of this phenomenon may lead to an alternative entry criterion for this small group of patients. For the moment, we still think it is acceptable to exclude ANA-negative patients from clinical trials.

Molecular classification criteria were also considered during the development of these criteria (29). Many novel biomarkers were

Table 4. Operating characteristics of the new classification criteria compared with the ACR 1997 and SLICC 2012 classification criteria in the derivation and the validation cohorts*

	ACR 1997 criteria	SLICC 2012 criteria	EULAR/ACR 2019 criteria
Derivation			
Sensitivity (95% CI)	0.85 (0.81–0.88)	0.97 (0.95–0.98)	0.98 (0.97–0.99)
Specificity (95% CI)	0.95 (0.93–0.97)	0.90 (0.87–0.92)	0.96 (0.95–0.98)
Combined (95% CI)	1.80 (1.76–1.83)	1.87 (1.84–1.90)	1.94 (1.92–1.96)
Validation			
Sensitivity (95% CI)	0.83 (0.80–0.85)	0.97 (0.95–0.98)	0.96 (0.95–0.98)
Specificity (95% CI)	0.93 (0.91–0.95)	0.84 (0.80–0.87)	0.93 (0.91–0.95)
Combined (95% CI)	1.76 (1.73–1.80)	1.80 (1.77–1.84)	1.90 (1.87–1.92)

* ACR = American College of Rheumatology; SLICC = Systemic Lupus International Collaborating Clinics; EULAR = European League Against Rheumatism; 95% CI = 95% confidence interval.

nominated, such as increased circulating B lymphocyte stimulator (BLyS), interferon-γ (IFNγ)–induced protein 10 kd (IP-10), monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor α (TNFα), type I IFN signature, or increased Th17 and plasma cell populations. They were all voted out in the expert Delphi exercise, largely because of limited availability in the clinical setting and/or insufficient evidence (5). However, inclusion of novel biomarkers, beyond autoantibodies, may ultimately further improve the specificity of SLE classification, increase alignment of classification with underlying disease pathogenesis, and improve the performance and information content of clinical trials. Thus, testing of biomarkers against these criteria is an important area for future research.

A new clinical criterion, unexplained fever, turned out to be common and remarkably characteristic for SLE. However, since infections are a major cause of death in SLE, it is of utmost importance to stress that fever, like all other criteria manifestations, should only be counted if no better explanation exists, and that infections have to be suspected first in any patient with (potential) SLE, particularly when C-reactive protein is elevated (30). The concept that all criteria are only to be counted if SLE is thought to be the most likely cause of the manifestation (i.e., no other more likely cause exists) is central to these new EULAR/ACR criteria, and is explicitly stated as an overarching principle. Some criteria, such as delirium, psychosis, and acute pericarditis, were in part redefined based on existing scientific definitions (22). Where alternative definitions were used, the performance of the alternative definitions was comparatively evaluated in the derivation cohort.

The differential weighting of criteria better represents their relative contribution to an individual's classification of SLE. For SLE, renal biopsy with class III or IV lupus nephritis carries the most weight and in the presence of a positive ANA is enough to classify a patient as SLE. This further develops a concept of the SLICC criteria (9) and reflects the current thinking of SLE experts; in the Delphi exercise, 85% would classify SLE on renal pathology alone (17). Renal biopsy with class II or V lupus nephritis still carries a large weight (8 points) but is not by itself sufficient for the classification of SLE.

The numerical goal of this project was to keep the specificity similar to the specificity of the ACR 1997 criteria, but increase the sensitivity to the high sensitivity level of the SLICC criteria, if possible. The validation cohort data suggest that this goal has been achieved. From our data, it appears that the SLICC criteria increase in sensitivity was to a significant degree founded in accepting renal histology and adding subacute cutaneous lupus and low complement levels. These three advances are mirrored in the current criteria. Many of the other additional symptoms of the SLICC criteria were of very low frequency. Specificity was increased by weighting of criteria, by the NGT expert panel decision to not allow lymphopenia to go forward, and, importantly, by the decision that no criterion be counted if better explained by another condition.

The new criteria provide a simple, directed, and highly accurate method for classifying SLE. An electronic "app" is in preparation, which will assist in the use of these criteria. However, it is important to stress that classification criteria are not designed for diagnosis or treatment decisions (5). They should never be used to exclude patients who do not fully meet these criteria from receiving appropriate therapies. This is also pertinent to patients with ANA-negative SLE discussed above. Diagnosis of SLE remains the purview of an appropriately trained physician evaluating an individual patient (5).

The new SLE classification system also provides new research opportunities. With much interest in early or latent SLE (31,32), the additive point system and the relative probability of classification it produces allows for systematic study of individuals who fall below the classification threshold. This will facilitate studies of disease evolution and early intervention. Furthermore, the use of an additive scoring system will allow for studying the idea of "ominousity," that is, the potential implications of having very high scores on disease severity and subsequent prognosis. This work would need to reconsider the

relative contribution of individual criteria (weights) and consider additional criteria that potentially contribute to ominousity.

It is anticipated that other groups will test these criteria, which will constitute important external validation. This will be particularly important for pediatric SLE and those with organ-dominant, for example, skin-dominant, disease, since it is a limitation of this criteria project that the patient cohorts do not represent these subgroups. Similar limitations also pertain to several racial/ethnic groups (for example, African American/Black, Hispanic, and Asian patients) and to men with SLE, each only included in lower numbers (Table 3). It is important to independently test the EULAR/ACR criteria in these subgroups. Leukocyte counts, for example, are more frequently below 4,000/mm^3 in African Americans (33), which may have an influence on criteria performance. It is also possible that the academic center patient populations included differ from patients in community practice clinics. Investigators testing the new criteria in different populations are reminded about the critical importance of the correct attribution of each criterion. Criteria can only be counted when not better explained by another condition (see Supplementary Table 2, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40930/abstract). The attribution process requires diligence and clinical experience.

In summary, our multiphase methodologic approach and ensuing classification system using ANA as an entry criterion and weighted, hierarchically clustered criteria constitute a paradigm shift in the classification of SLE. These criteria have excellent performance characteristics and face validity, as the structure and weighting were designed to reflect current thinking about SLE. The inclusion of fever assists with the classification of early SLE. The separation of renal biopsy findings reflects their differential impact on the probability of SLE classification. These criteria have strong operating characteristics, with excellent sensitivity and specificity. This classification system was built using rigorous methodology that was both data-driven and expert-based. With the inclusion of over 200 SLE experts from multiple countries and medical disciplines, methodologists, patient advocates, and over 4,000 subjects, this work is the largest international, collaborative SLE classification effort to date.

ACKNOWLEDGMENTS

The authors wish to acknowledge the diligent work of Banita Aggarwal and Keshini Devakandan in data entry, data cleaning, queries to submitting investigators, data cutting, and maintenance of the derivation and validation cohorts; and of Corine Sinnette, MA in the preparatory work for the multicriteria decision analysis exercise.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Aringer and Johnson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Aringer, Costenbader, Daikh, Brinks, Mosca, Ramsey-Goldman, Smolen, Wofsy, Boumpas, Kamen, Jayne, Naden, Dörner, Johnson.

Acquisition of data. Aringer, Costenbader, Daikh, Mosca, Bertsias, Hoyer, Leuchten, Tani, Tedeschi, Touma, Schmajuk, Anic, Assan, Chan, Clarke, Crow, Czirják, Doria, Graninger, Halda-Kiss, Hasni, Izmirly, Jung, Kumánovics, Mariette, Padjen, Pego-Reigosa, Romero-Díaz, Rúa-Figueroa Fernández, Seror, Stummvoll, Tanaka, Tektonidou, Vasconcelos, Vital, Wallace, Yavuz, Meroni, Fritzler, Naden, Dörner, Johnson.

Analysis and interpretation of data. Aringer, Costenbader, Daikh, Brinks, Mosca, Ramsey-Goldman, Smolen, Wofsy, Boumpas, Kamen, Jayne, Cervera, Costedoat-Chalumeau, Diamond, Gladman, Hahn, Hiepe, Jacobsen, Khanna, Lerstrøm, Massarotti, McCune, Ruiz-Irastorza, Sanchez-Guerrero, Schneider, Urowitz, Bertsias, Hoyer, Leuchten, Tani, Tedeschi, Touma, Schmajuk, Meroni, Fritzler, Naden, Dörner, Johnson.

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Journal of Autoimmunity
Volume 132, October 2022, 102845

Advances in SLE classification criteria

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Abstract

This year, the American College of Rheumatology (ACR) 1982 classification criteria for systemic lupus erythematosus (SLE) celebrate their 40th anniversary. From this start, the quest for optimal SLE criteria has led to the 1997 ACR update, the 2012 publication of the Systemic Lupus International Collaborating Clinics (SLICC) criteria, and, in 2019, the European League Against Rheumatism (EULAR)/ACR classification criteria. The latter have since been externally validated in more than two dozen studies and have become the gold standard inclusion criterion of SLE clinical trials. This comprehensive review attempts to follow the evolving success story of SLE classification, highlighting relevant decisions and their rationale, and discussing consequences for the way SLE is defined and managed.

Introduction

This year, 2022, sees the 40th anniversary of the publication of the 1982 American College of Rheumatology (ACR) classification criteria [1] and the 25th anniversary of their 1997 update [2], the 10th anniversary of the publication of the systemic lupus international collaborating clinics (SLICC) classification criteria [3] – and the 3rd anniversary of the publication of the European League Against Rheumatism (EULAR)/ACR classification criteria [4,5] for systemic lupus erythematosus (SLE). Accordingly, this is a

good timepoint to review SLE classification over the last forty years, which we consider an ongoing success story.

SLE is a challenging disease, both with regard to defining the entity in a clinically meaningful way, and with regard to devising classification criteria that are both specific and sensitive [6]. All of the four sets have been successful in the later, as shown in Table 1, which depicts the final sensitivities and specificities reported in the respective original publications – with the ACR 1997 update only validated later by the SLICC [3] and EULAR/ACR [4,5] efforts.

Beyond providing a necessary tool in defining a set of SLE patients for clinical trials, observational and translational studies on SLE, the criteria have also continuously shaped our picture of the disease. That said, it is important to reiterate that classification criteria are not what should decide on the individual diagnosis in a patient [7]. By necessity, they are designed to work on a group rather than on an individual level, and they need to simplify in order to remain practical tools. In consequence, there will be individual patients with SLE who do not fulfill the classification criteria, but still should be diagnosed with SLE, to receive proper treatment. Usually of lesser impact on the patient, there will also be patients fulfilling SLE classification criteria who suffer from conditions other than SLE. Accordingly, the diagnosis must remain with the properly trained physician [4,5], and treatment must not be limited to SLE patients fulfilling classification criteria.

Section snippets

Common ground

Before going into the development of the various sets of criteria, it appears sensible to explicitly look at the general rules that remained in place for all of them. The ACR 1982 criteria publication [1] defined “A person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.” In the SLICC criteria publication [3] this is worded “Criteria are cumulative and need not be present…

Criteria development over time

Since the early 1980s, there has been significant accrual of methodological knowledge on classification criteria development and how to avoid pitfalls that may lead to biased classification of patients [[8], [9], [10], [11], [12]]. Particularly, provisions were made to

avoid circular reasoning and self-fulfilling prophecies. In consequence, classification criteria projects have become ever bigger and more complex. This tendency can also be seen in the facts concerning the three major SLE…

The 1982 ACR criteria for SLE

Although there had been earlier efforts, the 1982 ACR criteria by Dr. Eng Tan and colleagues [1] arguably are the prototypical set of SLE classification criteria. The 4 in 11-item structure that resulted from these criteria could almost be said to have become so classical that the numbers were linked to the disease concept. For generations of physicians this set of criteria has shaped the picture of what is SLE.

The subcommittee analyzed the variables of the 1971 preliminary SLE criteria [13],…

The 1997 ACR criteria update

Shortly after the publication of the ACR criteria in 1982, anti-phospholipid antibodies were identified. The ACR criteria 1997 update [2] appropriately refers to Dr. Graham Hughes and Dr. Donato Alarcon-Segovia among others, citing a total of four pivotal publications [[14], [15], [16], [17]] and a paper by Piette and colleagues [18] suggesting reevaluation of the ACR criteria in this direction. At the same time, the LE cell test, which was available for less than half of the SLE patients…

The SLICC criteria

The SLICC group addressed a variety of concerns, which clinically included correlated terms relating to cutaneous lupus (such as malar rash and photosensitivity), the lack of inclusion of other cutaneous manifestations, the omission of neurologic manifestations, and the need for new standards in urinary protein quantification [3]. Immunologically, the omission of low complement levels, the need to include new information on anti-phospholipid antibodies, and above all the possibility to fulfill…

The EULAR/ACR criteria

From its beginning, the EULAR/ACR SLE classification project was based on ideas in three areas [6]. First, to maintain the specificity of the ACR criteria, while increasing sensitivity, and to enable early classification. Second, methodically, to follow a structure designed to maximize input, avoid circularity, and balance data and expert opinion. Third, contentwise, to test whether ANA could be repositioned as an entry criterion, based on its high sensitivity but low specificity, and to…

Information from the external validation of the EULAR/ACR criteria

Since the 2019 publication of the EULAR/ACR classification criteria, groups worldwide externally tested the new criteria. We performed a systematic literature review on PubMed with the string "(lupus OR SLE) AND criteria NOT review", which resulted in 4,409 citations. For the years 2019–2022, we extracted 92 abstracts. From 22 of these, the full publications contained information to at least derive an estimate for EULAR/ACR criteria sensitivity [40,[57], [58], [59], [60], [61], [62], [63], [64]…

Clinical trials

SLE clinical trials usually take several years, so that it is somewhat too early to expect published SLE clinical trials already using the EULAR/ACR 2019 criteria. With a search for recruiting phase 2 and phase 3 company trials on "lupus erythematosus, systemic" on clinicaltrials.gov↗, we found 39 trials listed as actively recruiting at the end of March 2022. For 26 of them, classification criteria were listed as inclusion criteria. In several of the remaining studies, patients were included by…

Lessons from criteria development on what SLE is

From the ACR 1982 criteria through the EULAR/ACR 2019 criteria it has held true that we do not have a unique laboratory parameter that defines who has SLE. ANA, which is at least sensitive enough to include almost all SLE patients, is clearly not specific enough to serve this purpose [37]. Antibodies to dsDNA, the next best guess, exclude around one quarter of patients with SLE [37], and when their sensitivity is forcefully increased, their specificity is prone to fall. While a meaningful…

Conclusions

The development of SLE classification criteria in the last forty years shows organic growth rather than radical breaks. Many of the clinical item concepts have remained in place over all this time. A few have entered the stage, such as SCLE and non-scarring alopecia with the SLICC criteria and fever with the EULAR/ACR criteria, and even fewer were given up over time. On approximately the same level, more immunological parameters were added, most prominently the complement components with the…

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Review paper

Reumatologia 2022; 60, 2: 125–132
DOI: https://doi.org/10.5114/reum.2022.115667

2022 Systemic lupus erythematosus remission in clinical practice. Message for Polish rheumatologists

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Abstract

Systemic lupus erythematosus (SLE) is a complicated multiorgan disease and can lead to organ damage and increased risk of morbidity and mortality. The strategy of management while avoiding complications, especially caused by chronic glucocorticoid therapy, improves outcomes. Different definitions of the treatment goal in different configurations of lupus activity indexes have appeared over the years. In 2021 the definition of remission and recommendations for its achievement were published and it become a way to implement a treat-to-target strategy. The main goal of treatment has become DORIS (definition of remission in SLE) remission and the alternative LLDAS (low lupus disease activity state).

Prolonging remission with clinical and immunological lupus activity restrictions and minimizing or stopping steroid doses reduced flares and damage accrual. The analysis and neutralization of poor prognosis predictive factors in lupus could be the most beneficial for less morbidity and mortality and better quality of life.

Key words: systemic lupus erythematosus, Systemic Lupus Erythematosus Disease Activity Index, DORIS remission, lupus low disease activity state.

Introduction

Systemic lupus erythematosus (SLE) is a very heterogeneous and complex autoimmunological disease sometimes difficult to recognize and treat. Tremendous diagnostic progress, wider awareness of consequences of damage, and new therapy development have significantly reduced mortality and improved prognosis. The risk factors for organ damage progression and factors of poor prognosis force us to use the most effective possible treatment.

Our clinical experience gives us the basis for more aggressive therapy when we are dealing with a severe course of the disease, lupus nephritis, or symptoms of organ damage already at the beginning of the lupus diagnosis. Irreversible organs damage is a cause of permanent reduction in quality of life and disability of patients with SLE. We have evidence that one organ failure leads to another, regardless of disease activity control and treatment [1].

For more effective management, limited complications, and less progression of secondary organ damage we should identify the goal of the treatment. An easier and measurable target such as glycated hemoglobin A_{1c} (HBA_{1c}) and blood pressure in diabetes and hypertension respectively is more possible to adopt as a treatment goal. In lupus, this target is not simple and uncomplicated but regardless we must have a definition of the goal to achieve the best results to which we are striving.

Different definitions of remission in systemic lupus erythematosus

Due to heterogeneity in clinical and laboratory manifestations, SLE requires more complex measures of dis-

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Submitted: 15.02.2022; **Accepted:** 23.03.2022

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ease activity. The latest proposed definitions of remission used these composite algorithms based on lupus activity indices, patients' physical assessment, and glucocorticoid (GC) dosage.

Optimally expressed remission guarantees the patient reduced mortality, prolonged time to next flare or quiescence of the disease, and, most importantly, no organ damage. Complete remission should be our most preferred, but often the most restrictive treatment goal.

Previous longitudinal studies revealed a wide range of prevalence of different definitions of remission [2–4]. Authors reported that those who achieved remission had less lupus activity and a better prognosis over 5–10 years.

Despite a better understanding of lupus pathogenesis, immunology and clinical phenotypes of lupus patients there remain many unmet needs in developing innovative therapies that can potentially limit damage accrual.

However, for safer and more effective treatments to develop, to define treatment goals disease activity assessment tools are needed. In rheumatology in the field of rheumatoid arthritis or psoriatic arthritis, the treat-to-target strategy is used with positive effects, although it has not been proven in lupus.

An ideal therapeutic target is a remission defined and measured by validated tools for assessing disease activity. What does it mean in lupus? What is the most objective tool to consider and how to define remission in SLE? There remain difficult questions.

The discussion about the definition of remission in SLE has been going on for several years. Sustained state without signs and symptoms, quality of life level, fewer flares, lack of immunological activity – what is the definition of the treatment goal?

Different definitions of remission took into account lupus activity assessment indicators such as the SLEDAI score, physical global assessment (PGA), and kind of lupus treatment. These components were used in miscellaneous combinations with various cutoffs and therefore their comparison is impossible in terms of treatment effectiveness, especially innovative targeted therapies in clinical trials.

A cross-section survey of various combinations of definitions of remission was examined by Saccon et al. [5]. These data revealed the most common and the strongest goal in lupus from eight proposed and examined definitions according to the DORIS (definition of remission in SLE) framework [6].

Clinical SLEDAI (clinical Systemic Lupus Erythematosus Disease Activity Index 2000 – cSLEDAI) proved the most achievable goal in lupus in this extremely detailed study. Clinical SLEDAI is a variant of the lupus scale that does not take into account serology results and allows the use of antimalarials, low doses of GCs, and immunosuppressives (ISs) including biologicals.

Despite the lack of clinical activity of lupus, immune activity, i.e. increased antibody concentrations of anti-dsDNA, and decreased C3 and/or C4 complements, may indicate disease activity. Serologically active clinically quiescent disease, well described in the published literature, could be a sustained state without increased risk of flares and damage in summarized evidence [2, 7, 8].

Indeed, being aware of great developments in such fields as immunology and genetics, we are still looking for a biomarker of treatment efficacy, responder to targeted therapy, or predictors of poor outcomes [9]. Abnormal serology in SLE has been discussed by many researchers, and in most studies, immunological activity was not an independent predictor of damage, late morbidity, or mortality [10].

Another aspect of the construction of the final definition of remission was the influence of lupus therapy and its effect on disease activity, the safety of treatment, and the avoidance of dependent complications. Especially GCs and their advantages and disadvantages of chronic use are still discussed. Prednisone doses between 6 and 12 mg per day increase major organ damage by 50% [11].

Our knowledge is growing about increased mortality because of glucocorticoid-dependent damage, and our awareness is growing, which is visible in a significant decrease in mortality in the last decade. The evolution of treatment strategy has become a reality but its goal was not clearly defined.

The final recommendations from the International Task Force appeared in 2021 and constitute a summary of the discussions to date and consensus on a definition of remission in SLE (DORIS) [12]. The recommendations are a guide for clinicians, scientists, and researchers for better defining remission achievement and treat-to-target strategy implementation in patients with SLE.

The treat-to-target strategy improves outcomes in inflammatory diseases and strict targeting in lupus may improve patients' prognosis in the long term.

Treat-to-target strategy

The experience of the last decade of clinical practice has shown that the treat-to-target strategy led to improved care for patients with inflammatory rheumatic diseases.

The treatment strategy of any disease should be structured and targeted to achieve objectives that deliver long-term benefits. It is obvious that establishing a measurable, efficacious, validated treatment endpoint

for assessing remission in a multi-organ disease such as SLE is very complicated.

However, we know that the benefits for lupus patients outweigh any problems or difficulties in long-term perspectives. A goal-directed treatment approach has a profound impact on the management of chronic inflammatory diseases.

Rheumatologists learn from the experience of activity assessment in rheumatoid arthritis (RA). Lessens from RA give the proof that instruments using both clinical judgment and laboratory results indisputably improve outcomes by more effective standard treatment [13].

The fluctuating nature of SLE, relapsing-remitting disease with flares or persistently active disease, leads to irreversible organ damage such as stroke, heart infarction, end-stage renal failure, or glucocorticoid-dependent osteoporosis or cataract [14–16].

Moreover, the quality of life dramatically decreases due to our lack of vigilance and elimination of known risk factors. Both issues, high disease activity level due to poor control with damage progression, and chronic GC treatment with all the consequences, are responsible for the high mortality rate in SLE. Target definition in systemic lupus is expected to help reduce organ damage, improve long-term treatment outcomes and ultimately reduce mortality [17, 18].

The implementation of a treat-to-target strategy in lupus treatment is a very complicated process. It is determined not only by the limits of the remission definition items, but also by less measurable symptoms, pain, arthralgia, or fatigue.

Co-morbidities also affect the patient's condition or further impair the quality of life of lupus patients, such as depression secondary to disease or during neuropsychiatric manifestations. Management according to the treat-to-target strategy in lupus requires greater clinical knowledge and insight, efficiency, and determination in achieving the goal of disease remission.

Since 2012, international experts' work has been underway to define remission as part of the treat-to-target strategy in lupus. Our management and therapy in lupus depend on these essential activities which have become a basis of a treat-to-target strategy (Fig. 1).

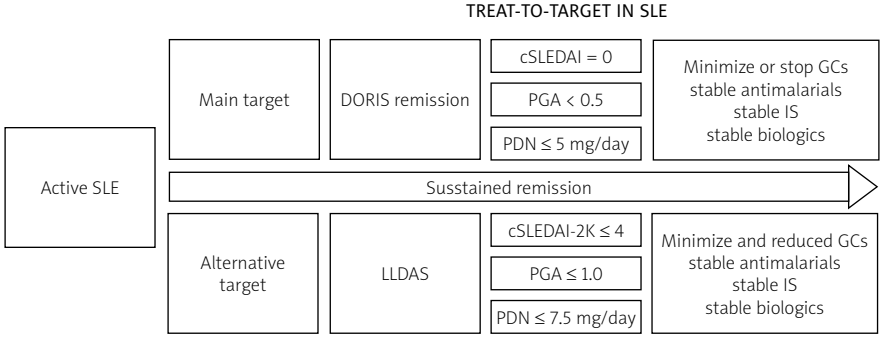
Numerous definitions have been explored in terms of duration and reduction in risk of damage, but currently the DORIS (definition of remission in SLE) remission and LLDAS (lupus low disease activity state) appear to be the most reliable and achievable goals [12, 19].

Definition of systemic lupus erythematosus remission, 2021

In 2016 an international task force published a framework for DORIS definition without final recommendations [6]. To meet the expectations in November 2021 the final recommendations were published and a simplified and universal definition was created that can be applied in clinical practice [12].

The International Task Force DORIS described remission as a complex of factors measured by cSLEDAI which does not take into consideration serology results, PGA to reflect the patient's perspective, and the dose of prednisone (PDN) as a factor affecting the risk of long-term organ damage.

Remission recommended by the DORIS task force is defined by cSLEDAI = 0, PGA < 0.5 points, and PDN ≤ 5 mg per day. The Systemic Lupus Erythematosus Disease Activity Index score is included in the global score system, which provides an overall measure of lupus activity alongside the European Consensus Lupus Activity Measurements SLAM (Systemic Lupus Activity Measure) [20] and, more complicated and difficult to



cSLEDAI – clinical Systemic Lupus Erytematosus Disease Activity Index, GCs – glucocorticosteroids, IS – immunosuppressives, LLDAS – lupus low disease activity state, PGA – Physical Global Assessment, PDN – prednisone.

Fig. 1. Remission treat-to-target strategy in systemic lupus erythematosus.

apply, the individual organ assessment British Isles Lupus Assessment Group Index (BILAG) [21].

Evaluation of lupus activity by SLEDAI score requires the application of certain principles, but most of the points of assessment are not objective and depend on clinical judgment. It follows that we do not have independent tools for lupus assessment activity. Similar doubts apply to PGA, which reflects the health-related quality of life from patients' perspectives.

Nevertheless, remission by any definition is associated with improving quality of life, which is the most important factor for patients with SLE. The principle of lupus treatment for rheumatologists who deal with guiding the patient should be minimizing GCs doses, and this is our direct goal in the definition not only of DORIS remission. Maintaining standard treatment during remission by ISs and/or biologics is necessary and antimalarials are allowed.

The most restrictive definition and most expected clinical condition is DORIS complete remission with no clinical and serological activity (SLEDAI = 0) with PGA below 0.5 points and with maintenance antimalarial therapy without the need for any dosage of GCs and IS or biologics.

The frequency of SLE remission in available data and clinical practice is not high and is still insufficient. In the literature, many propositions of alternative, more achievable goals have been presented.

Remission key messages are shown in Table I.

Table I. Remission key messages

Remission is an achievable and desirable target in SLE and a part of the treat-to-target strategy which can be applied in clinical practice
Optimally expressed remission guaranteeing the patient reduced mortality, prolonged time to next flare and the most important no organ damage
Chronic GCs therapy is a major independent predictor organ damage accrual. The principle of lupus treatment for rheumatologists should be minimizing or consider withdrawing GCs treatment
The final recommendations 2021 constitute a summary and consensus on a definition of remission in SLE – DORIS remission
Lupus low disease activity state is alternative target which is a compromise between achievable therapeutic effects and minimizing GCs doses

Low systemic lupus erythematosus activity

Multiple studies based on multiethnic and multicenter cohorts evaluated lupus activity according to alternative targets before the DORIS recommendations for remission were published. We have several definitions of low disease activity widely described in the literature.

The term low disease activity (LDA) was defined by Toronto Lupus Cohort investigators and included cSLEDAI ≤ 2 points (without serology results index) and in the most restrictive treatment rules GCs and IS exclusion [22].

The remission objective proposed by Franklyn et al. [23], low lupus disease activity state (LLDAS), is a potential alternative target in our lupus treatment strategy. Among the components of the definition of LLDAS are SLEDAI-2K ≤ 4 points and PGA ≤ 1.0 points, and a minimal dose of PDN ≤ 7.5 mg per day. In remission by LLDAS definition, an additional criterion of any clinical or serological activity must be met.

Due to the level of listed indicators reflecting disease activity, this definition represents a compromise between achievable therapeutic effects and minimizing GC doses. The strongest evidence refers to time-dependent reducing disease flares and organ damage accrual in patients with remission determined by LLDAS definition [23, 24]. Consequently reduced damage progression is associated with decreased mortality by almost 70% as well as improving patient outcomes [25].

Furthermore, based on post-hoc analysis of innovative therapies in SLE, belimumab or anifrolumab, we know that LLDAS has a potential validated outcome measure in clinical trials [26, 27].

Prevalence, predictors and prognostic benefits of remission

Prevalence of remission depends on management and utilized available treatment options and is still an unmet need in the population of lupus patients. In the therapy of systemic lupus, we are aware of the limited effectiveness of possible treatments and problems with prevention flares, persistently active disease, and damage accrual.

Previous studies have revealed that especially the initial years of the disease have implications for the propensity for flare or remission and they are predictive of long-term outcomes. More aggressive treatment for induction, consolidation, and maintenance of the remission state seems to be a good strategy but not so common and not always feasible. In the future perspectives, remission is a state we should strive for because of fewer complications, lower mortality, and better long-term outcomes.

The percentage of remission in different studies varies between 63 and 74.8% of LLDAS according to Tani et al. [28], and 44% in Asian-Pacific countries according to Golder et al. [24]. Different potential definitions and

their impact on capturing the remission state and predicting damage by the SLICC/ACR Damage Index were described by Saccon et al. [5].

As mentioned in the introduction, in this Italian multicenter study, a 69.2% remission rate according to the DORIS definition was noted. Various definitions examined in this study were based on single or a combination of remission items such as SLEDAI score, PGA, and PDN doses [6, 12].

The most attainable definition to meet was cSLEDAI, which in BLISS trials, provided with antibodies against B-lymphocyte stimulator (BLyS) in SLE, was shown to be a target and clinical positive endpoint of belimumab treatment. Clinical SLEDAI is only one component of remission assessment by both LLDAS and DORIS definitions. Low lupus disease activity state is easier to achieve than DORIS remission, and it is related to PDN doses but also patients' self-assessment by PGA.

Discussion about remission with and without treatment, especially GCs, is a very important point of consideration by experts. Complete cure of the disease is an obvious target for management and treatment in any disease, but in SLE, as a chronic disease, it is not reachable.

Although some predictors of damage are non-reversible, such as non-Caucasian ethnicity and older age, high lupus activity level and chronic GCs therapy directly associated with damage are possible to treat and reduce significantly. Moreover, with so much progress in the diagnostics and treatment of SLE, predictive factors help us to adjust the level of the treatment to achieve the best long-term results.

Definitions of remission in SLE and LLDAS remission have been compared in the field of reducing flares and damage progression in various studies [29, 30]. Based on these data, attempts were made to reach a definite conclusion that deeper and longer remission is associated with stronger protective effects against organ damage and its consequences. The remission achieved by maintenance therapy in different published data is in the range of 25–37% [17, 31, 32].

Evidence from observational studies shows that in the populations of South and North America, Asia, and especially Europe, prolonged DORIS remission on treatment was associated with reduced damage accrual [3, 31, 33, 34].

A complete remission requiring no therapy is very rare in both research and clinical practice, and even more unique given the length of remission. In a Canadian study patients with 5 consecutive years of complete remission not requiring medication accounted for 1.7% of the whole cohort [35] and in other analyses did not exceed 7% [3, 4].

Nevertheless, prolonged drug-free remission is very rare and difficult to achieve in studies but also in clinical practice. First of all, the most important goal reduction of damage accrual and increasing time to flare depends on remission duration and its level [5, 4].

Duration of remission was a key point to consider in published data, because of its association with reduced organ damage. In numerous studies published by Zen et al. [3, 36] Caucasian SLE patients were protected against damage after at least two consecutive years in remission but better outcomes in damage accrual were achieved after prolonged maintained remission defined over 5 years.

However, data from the largest US population DORIS and LLDAS remission studies published by Petri et al. [17] have shown that reducing the risk of long-term damage is possible even with a lower percentage of time in LLDAS on treatment.

The difficulties with remission achievement in such a complicated, heterogeneous disease mean that any period of low SLE activity, especially remission, is an achievement with measurable long-term benefits [5, 22].

A review of 41 SLE studies with over 17 thousand patients revealed the percentage of achieving at least one year of maintained remission as 42.4% to 88% and remission predictors associated with lower accrual of organ damage and better quality of life among lupus patients. In this systemic review, the predictive factors older age at diagnosis, lower baseline SLE activity, and absence of major organ involvement were identified; however, positive serology results were negatively associated with remission [37].

Especially prolonged remission is an achievable and desirable target, and we have multiple proofs that are associated with benefits. Consequently, the path to achieving these benefits should be determined by the principles of treatment.

Chronic GC therapy followed by evidence is a major independent predictor of organ damage accrual in addition to typical steroid-dependent complications such as diabetes, osteoporosis, avascular necrosis, or cataract [15, 38].

Nowadays, with so much knowledge on complications of GCs therapy available, restriction of GCs use seems to be the overriding principle. Unfortunately, tapering and withdrawal of GCs before immunosuppressive therapy to protect against flare and organ damage according to recommendations is not a routine good clinical practice everywhere [16, 39, 40].

Achieving long-term remission and the decision to discontinue GCs therapy do not result in an increased risk of flare, interestingly even in lupus nephritis, where decisions to withdraw GCs and ISs could be more predisposing to an exacerbation [41, 42].

A low level of SLE activity according to DORIS remission or LLDAS is the ideal situation to consider tapering or withdrawing treatment after assessment of the time of recent disease flare and risk factors. The physician's decision depends on clinical judgment and a good patient's condition; nevertheless, it may not be disturbed by clinically irrelevant symptoms such as arthralgia, pain, or fatigue. Most of the SLE patients after treatment-induced sustained remission discontinued GCs successfully while only a minority of patients had non-significant manifestations.

Tani et al. [42] presented the frequency range of 2.4–50% of GCs-free SLE patients in the cohorts reported in the literature. In this study, of patients who achieved remission and had GCs treatment discontinued, flares occurred in 23% of SLE patients at 2 years; by comparison, in the group of patients who required GCs maintenance therapy, most of the patients (69.8%) had at least one flare during 6 years of follow-up. These data revealed the point of going into GCs-free remission even if this goal required effort to achieve it.

Immunosuppressive therapy was a basic treatment in the context of induction and consolidation of remission. According to recommendations, IS discontinuation should be the next step after GCs tapering or withdrawal following disease activity control. Flares after stopping prolonged ISs are not uncommon although antimalarial treatment can reduce the risk and bring benefits.

Hydroxychloroquine (HCQ) is a cornerstone of SLE therapy and a very important factor especially in a discussion about remission. Consistent antimalarial treatment reduced the risk of flares [43] and, more importantly, mortality [44, 45], and during remission is a beneficial and desirable treatment. The definitions of remission allow the use of chloroquine (CQ) or HCQ for disease activity control.

Despite still limited treatment options in SLE, remission regardless of definition is an achievable goal and reducing the risk of damage and progressive destructive disease depends on our awareness of GCs prolonged overtreatment, sustained HCQ, and reasonable immunosuppressive therapy. The best objective decisions for the SLE patient are made in the longterm perspective, taking into account the risks and benefits of the treatment and management including prognostic predictive factors.

Conclusions

The treat-to-target strategy in rheumatology improved outcomes and should be a key to success in the management of SLE patients. The construction of the definition proper of the treatment goal was an achievement in SLE and has the potential for limitation of organ damage accrual.

Reduction of flares and damage accrual is possible with sustained prolonged remission. Remission components, in any definitions of DORIS or LLDAS, revealed reduced overall activity levels, low SLE activity in cSLEDAI assessed by a physician, good condition in PGA score assessed by patients, and a low dose of GCs with basic antimalarial therapy, ISs, and/or biologics.

Successful implementation of DORIS remission and LLDAS definition as a treatment goal allow the adoption of a treat-to-target strategy for greater damage protection in clinical practice. Chronic GCs treatment is the most dangerous predictor of poor prognosis, an independent risk factor of organ damage in the course of SLE.

The aggressive effective treatment of SLE flares by a high dose of GCs and strong ISs in induction therapy, consolidation of clinical improvement, and achieving prolonged, sustained remission is a way for withdrawing GCs and avoiding complications. The deeper and longer the remission is, the stronger is the protective effect, with less morbidity and mortality, and better long-term outcomes.

The authors declare no conflict of interest.

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RHEUMATOLOGY

Rheumatology 2018;57:e1–e45
doi:10.1093/rheumatology/kex286
Advance Access publication 6 October 2017

Guidelines

BRITISH SOCIETY FOR RHEUMATOLOGY

The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults

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Key words: lupus, diagnosis, assessment, monitoring, management, immunosuppressants, treatment, efficacy, non-biologics, biologics.

Scope and purpose of the guideline

Background

SLE (or lupus for short) is a multisystem, autoimmune disease, involving complex pathogenetic mechanisms that can present at any age. It most commonly presents in women in the reproductive age group, although lupus is increasingly recognized after the age of 40 years, particularly in Europeans [1–3]. Lupus affected nearly 1 in 1000 of the population in the UK in 2012 [4] and was

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NICE has accredited the process used by the BSR to produce its guidance on the management of systemic lupus erythematosus in adults. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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Submitted 29 July 2016; revised version accepted 16 June 2017

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most frequently observed in people of African-Caribbean and South Asian descent [4–6]. The age-standardized incidence in the UK according to the Clinical Practice Research Datalink is 8.3/100 000/year for females and 1.4/100 000/year for males [4], and the highest incidence rates are seen in those of African-Caribbean descent: 31.4/100 000/year, compared with 6.7/100 000/year for those of white European descent. The mean age at diagnosis is 48.9 years [4], but it is lower in those of African ancestry in the UK [4–6] and North America [2, 7].

The disease is prone to relapses and remissions, resulting in considerable morbidity due to flares of disease activity and accumulated damage, and an increased risk of premature death, mostly due to infection or cardiovascular disease [2, 8–14]. Death from active lupus is rare in the UK [15, 16]; however, a 10% mortality over 20 years and a mean age of death of 53.7 years was recently reported [16]. About one-third of SLE patients in the UK develop LN [16–18]. Patients of African ancestry tend to present young with LN in the UK, as in the USA and elsewhere [2, 17, 19], and are at considerable risk of developing end-stage renal disease (ESRD) and of dying prematurely. In another UK cohort, ESRD occurred in 20% of LN patients within 10 years of diagnosis, and the mean age at death in LN patients was 40.3 years, with an average of 7.5 years between development of LN and death [18].

The mainstay of therapy for active lupus until recently has been NSAIDs, CSs, antimalarials such as HCQ, and immunosuppressants such as AZA and CYC, although only prednisolone and HCQ are licensed for lupus [8, 20]. With the exception of LN, there were relatively few trials until the last 15 years, and in 2011, belimumab became the first drug to be licensed for the treatment of active lupus for over 50 years [20]. New therapies that will reduce the need for CSs to control lupus activity and to reduce the development of damage and infection are needed to improve outcome [10–12, 16, 21]. In the meantime it is important to manage patients optimally with the treatment strategies that are available.

Need for the guideline

Despite some improvement in survival data over the last 40 years [2, 13], lupus patients still die on average 25 years earlier than the mean for women and men in the UK [16]. The disease can present with slowly or rapidly progressive active disease at any age and can be associated with the rapid accumulation of damage if not promptly diagnosed, appropriately treated and regularly monitored [2, 8, 14, 19, 20]. An up-to-date comprehensive guideline to optimize these aspects of management that is consistent with current evidence and National Health Service (NHS) practice is warranted to improve the outcome of this variable and potentially life-threatening disease that

Table 1 Levels of evidence and grades of recommendation for diagnosis, assessment and monitoring of non-renal SLE

Statement/item	Number of studies	Overall SIGN level of evidence	Grade of recommendation	Selected references covering items discussed in text
Diagnosis from clinical and serological features				
Prognostic value of:				
Clinical features	29	2++	B	[7, 10, 26–35]
ANA	8	2++	B	[26–29, 34, 36–38]
Anti-dsDNA antibodies	17	2++	B	[26–29, 37, 39, 40]
Low C3/C4 levels	13	2+	C	[27, 41–46]
Anti-Ro/La antibodies	4	2+	C	[10, 27–29, 37]
aPLs	12	2++	B	[26, 27, 29, 47]
Assessment and monitoring of SLE disease activity and damage				
Clinical flare	6	2+	C	[48, 49]
Good diagnostic utility of:				
clinical and laboratory monitoring	28	2++	B	[11, 16, 21, 32, 50–57]
anti-dsDNA and C3/C4 levels	14	2++	B	[40, 43, 44, 46, 49, 58–60, 61–63]
aPL repeat	–	–	D	[47]
anti-Ro/La for neonatal lupus	6	1+	A	[64, 65]
CRP low or normal unless infection	4	2++	B	[66–69]
ESR correlates with active lupus	2	2+	C	[69, 70]
Prognostic value of lupus disease activity and damage indices	>60	2++	B	Reviewed in [12, 71] [11, 14–16, 32, 72, 73]
Monitoring and treating cardiovascular risk factors in SLE patients	6	2+	C	Reviewed in [22, 71, 74–76]
Frequency of monitoring SLE:				
For active disease, every 1–3 months after diagnosis or flare	2	2+	C	[72, 77]
Low/no disease activity, stable treatment: 6- to 12-monthly	–	–	D	Expert opinion
Monitoring for drug toxicity/levels	2	2+	C	[78, 79]

SIGN: Scottish Intercollegiate Guidelines Network

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Table 2 Levels of evidence and grades of recommendation for medications used in the treatment of non-renal SLE

Treatment (recommended target dosage)	Main uses (unless contra-indications)	Total number of papers	Overall SIGN level of evidence	Grade of recommendation	Comments: including number of reports and references for RCTs, cohort studies and systematic reviews/meta-analyses (SRs)
Antimalarials: HCQ $\leqslant$6.5 mg/kg/day	Mild lupus, prevent flare in all patients, prevent damage, steroid-sparing	45	1 ++	A	7 RCTs [80–86]; 36 cohort studies [87–120]; 2 SRs [121, 122]
MTX $\leqslant$25 mg/week	Mild and moderate lupus, prevent flare, steroid sparing	12	1+	A	2 blind, 1 open-label RCTs [123–125]; 5 cohort studies [126–130]; 2 case series [131, 132]; 2 SRs [133, 319]
NSAIDs	Symptom control in mild non-renal lupus only	1	3	D	1 SR covers case series/reports [134]
Sunscreen (high-SPF UV-A and UV-B)	Prevents UV-induced rashes and other manifestations	7	2 ++	B	1 blind RCT [135]; 5 cohort studies [136–140]; 1 case series [141]
Low-dose oral prednisolone ($\leqslant$7.5 mg)	Mild lupus and to prevent flares	0	4	D	Expert opinion
Higher doses of oral prednisolone $\leqslant$0.5 mg/kg/day	Moderate lupus and prevention of flares	0 2	4 2+	D C	To prevent flare: 1 blind RCT [46] and 1 open-label RCT [60]
I.m. triamcinolone	Moderate lupus	1	2+	C	1 open-label RCT [142]
I.m. methylprednisolone (80–120 mg)	Moderate lupus	0	4	D	Expert opinion
I.v. methylprednisolone (100–250 mg)	Moderate lupus	1	2+	C/D	1 blind RCT for 100 mg *vs* 1000 mg [143]
I.v. methylprednisolone (500 mg–1 g) $\times$ 1–3 pulses	Moderate and severe lupus	6	2+	C	2 small blind RCTs [143, 144]; 1 open-label trial [145]; 3 cohort studies [146–148]
AZA (if TPMT normal) 2–3 mg/kg/day	Moderate lupus, prevent flare, steroid sparing	10	2+	C	4 open-label RCTs [149–152]; 5 cohort studies [153–157]; 1 case series [158]
MMF 2–3 g/day	Moderate/severe lupus, prevent flare, steroid-sparing	13	2 ++	B	3 open-label RCTs [159–161]; 7 cohort studies [162–168]; 1 case series [169]; 2 SRs [133, 170]
Mycophenolic acid/sodium 1.44–2.16 g/day	For patients intolerant of MMF	2	3	D	1 open-label RCT [171]; 1 cohort study [172]

(continued)

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Table 2 Continued

Treatment (recommended target dosage)	Main uses (unless contra-indications)	Total number of papers	Overall SIGN level of evidence	Grade of recommendation	Comments: including number of reports and references for RCTs, cohort studies and systematic reviews/meta-analyses (SRs)
Ciclosporin $\leqslant$2.5 mg/kg/day	Moderate/severe lupus including cytopenias, prevent flare, steroid-sparing	11	2+	C	2 open-label RCTs [152, 173]; 8 cohort studies [174–181]; 1 SR [133]
Tacrolimus 1–3 mg/day (assess drug levels)	Moderate/severe lupus, steroid-sparing	3	3	D	2 cohort studies [182, 183]; 1 SR [133]
LEF (20 mg/day)	Moderate lupus without subacute rash	3	3	D	1 small blind RCT [184]; 1 cohort study [185]; 1 SR [133]
CYC (see text for dosing)	Severe lupus, including NPSLE, prevent flare, steroid-sparing	30	2 ++	B	4 open-label RCTs [186–189]; 25 cohort studies covered by 1 SR [133]
Rituximab 1000 mg $\times$ 2	Refractory severe and moderate lupus; steroid-sparing	33	2+	C	1 blind RCT [190, 191]; 3 open-label RCTs [192–194]; 24 cohort studies [195–198 not in SRs]; 2 case series [194, 199]; 2 SRs, including 1 meta-analysis [200, 201]; 1 SR with 26 extra case reports/series [202]
Belimumab 10 mg/kg/4 weeks	Refractory moderate/severe lupus; prevent flare and steroid-sparing (not NPSLE)	5	1+	B	2 phase III blind RCTs [203, 204]; 1 phase II blind RCT [205]; *post hoc* combined analysis [206]; 1 open-label extension [207, 208]; 1 meta-analysis [209]
IVIG (see text)	Refractory severe lupus (including catastrophic APS)	19	2–	D	Rarely indicated: 3 open-label trials [210–212]; 10 cohort studies [213–222]; 4 case series [223–226]; 2 SRs with 1 meta-analysis [227, 228]
Plasmapharesis	TTP; refractory severe SLE	10	2 ++ for TTP; 3 otherwise	B for TTP; D otherwise	Rarely indicated: 9 cohort/case series [229–237]; 1SR [238]

TPMT: thiopurine S-methyltransferase (see text); TTP: thrombocytopaenic purpura.

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causes considerable morbidity. There have been no previous UK-based guidelines for lupus. The European (EULAR) recommendations for the management of lupus in general were not very detailed and were published in 2008 [22], although more specific recommendations were published for neuropsychiatric lupus in 2010 [23], and joint EULAR and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for LN were published in 2012 [24], as well as ACR guidelines for the management of LN in 2012 [25].

Objectives of the guideline

The aim of this guideline was to produce recommendations for the management of adult lupus patients in the UK that cover the diagnosis, assessment and monitoring of lupus and the treatment of mild, moderate and severe active lupus disease, but which do not imply a legal obligation. The resulting recommendations are based on an extensive review of the literature up to June 2015 to produce evidence-based guidelines, particularly for the treatment of non-renal lupus, supplemented as necessary by expert opinion and consensus agreement (Tables 1 and 2). The guideline development group recommended that patients with LN are managed according to the EULAR/ERA-EDTA recommendations for LN [24] and provide their strengths of agreement (SOAs) with a summary of the most important items in those recommendations (Table 3).

Target population, target audience and stakeholder involvement

The guidelines address the management of adult patients only and have been developed by a multidisciplinary guideline development group set up by the British Society for Rheumatology (BSR) and led by C.G., consisting of academic (C.G., I.N.B., D.D.C., M.K., D.I.) and NHS consultants in rheumatology (M.A., B.G.) and nephrology (D.J., L.L.), rheumatology trainees (M.G., K.S.), a GP (B.E.), a clinical nurse specialist (S.B.), a patient representative (Y.N.) and a lay member (P.N.). All participants declared any conflicts of interest and these are listed at the end of this article. The target audience includes rheumatologists and other clinicians such as nephrologists, immunologists and dermatologists, trainees in these specialties and emergency medicine, GPs, clinical nurse specialists and other allied health professionals involved in the care of adult lupus patients. Opinions of other key stakeholders such as other consultant members of the BSR, additional trainees, podiatrists, nurse specialists and representatives of Lupus UK were sought during the preparation of these guidelines.

Areas that the guideline does not cover

This guideline does not cover the evidence for topical or systemic therapy for isolated cutaneous lupus, nor does it discuss paediatric lupus, as there is relatively little literature on paediatric lupus. As the disease tends to come on after puberty, most of the recommendations are likely to be appropriate for children/adolescents, with suitable dose modifications. We provide only summary advice about the use of drugs in the management of pregnant lupus patients, and refer to the extensive review of drugs used in pregnancy and breast-feeding that have been recently published [239, 240]. The management of complications of lupus, including chronic fatigue, cardiovascular risk, osteoporosis, infection and cancer risk are not discussed in detail, as these issues should be managed as for other patients with similar risk factors according to national and international guidelines. Management of thrombosis will depend on whether or not the criteria for APS are met [241].

Rigor of development

Selection of questions for the literature review, and statement of extent of previous National Institute for Health and Care Excellence, Royal College of Physicians, and Scottish Intercollegiate Guidelines Network guidelines

A multidisciplinary guideline development group was formed and followed the BSR Protocol for Guidelines and EULAR standardized operating procedures to define the focus of the work, the target population and the target audience. Discussions were supplemented by consensus-building strategies, including a modified Delphi technique, in order to reduce and clearly define the list of research questions to be addressed by the literature search (see supplementary data section Search strategy, available at *Rheumatology* Online). There are no BSR, Royal College of Physicians (RCP), National Institute for Health and Care Excellence (NICE) or Scottish Intercollegiate Guidelines Network (SIGN) guidelines or recommendations for the management of lupus in the UK to help improve the outcome of this variable and potentially life-threatening disease, but lupus has been included in the on-line resource Map of Medicine.

Literature review: eligibility criteria and limitations of the search

A systematic search of MEDLINE (PubMed) and the Cochrane Database of Systematic Reviews was performed, and all publications in peer-reviewed English language journals up to June 2015 were considered. A detailed search was performed using an array of relevant terms (see supplementary data section Search strategy and supplementary Table S1, available at *Rheumatology* Online), and papers were screened for eligibility based on their title, abstract and/or full content. Studies were eligible if they had studied at least 50 patients for prevalence and prognosis of manifestations, 10 patients for diagnosis and monitoring, or 5 patients for therapy.

Studies on animals, children, review articles, commentaries, conference abstracts or statements, and expert opinion statements were excluded. Narrative review articles and existing guidelines were checked for references, but only meta-analyses and systematic reviews were included, together with original research articles, in the analysis. Over 8000 articles were identified during the literature search, and over 600 were deemed eligible for

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Table 3 Strength of agreement of authors with the main EULAR/ERA-EDTA recommendations for the management of LN

Management of SLE patients with renal involvement	SOA[a]
Assessment of renal involvement	
1. Indications for first renal biopsy in SLE	97
Any sign of renal involvement—in particular, urinary findings such as reproducible proteinuria $\geqslant$0.5 g/24 h, especially with glomerular haematuria and/or cellular casts—should be an indication for renal biopsy. Renal biopsy is indispensable since, in most cases, clinical, serologic and laboratory tests cannot accurately predict renal biopsy findings.	
2. Pathological assessment of kidney biopsy	98
The use of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system is recommended, with assessment not only of active and chronic glomerular and tubulointerstitial changes, but also of vascular lesions associated with aPLs/APS.	
Treatment of renal involvement	
3. Indications and goals of immunosuppressive treatment in LN	98
3.1 Initiation of immunosuppressive treatment should be guided by a diagnostic renal biopsy. Immunosuppressive agents are recommended in class III_A or $III_{A/C}$ ($\pm$V) and IV_A or $IV_{A/C}$ ($\pm$V) nephritis, and also in pure class V nephritis if proteinuria exceeds 1 g/24 h despite the optimal use of renin–angiotensin–aldosterone system blockers.	
3.2 The ultimate goals of treatment in LN are long-term preservation of renal function, prevention of disease flares, avoidance of treatment-related harms and improved quality of life and survival. Treatment should aim for complete renal response with UPCR <50 mg/mol and normal or near-normal (within 10% of normal GFR if previously abnormal) renal function. Partial renal response, defined as $\geqslant$ 50% reduction in proteinuria to subnephrotic levels and normal or near-normal renal function, should be achieved preferably by 6 months but no later than 12 months following initiation of treatment.	98
4. **Treatment of adult LN—initial treatment**	
4.1 For patients with class III_A or $III_{A/C}$ ($\pm$V) and class IV_A or $IV_{A/C}$ ($\pm$V) LN, mycophenolic acid (MPA) (MMF target dose: 3 g/day for 6 months, or MPA sodium at equivalent dose) or low-dose i.v. CYC (total dose 3 g over 3 months), in combination with glucocorticoids, are recommended as initial treatment as they have the best efficacy/toxicity ratio.	93
4.2 In patients with adverse prognostic factors (acute deterioration in renal function, substantial cellular crescents and/or fibrinoid necrosis), similar regimens may be used, but CYC can also be prescribed monthly at higher doses (0.75–1 g/m^2) for 6 months or orally (2–2.5 mg/kg/day) for 3 months.	92
4.3 To increase efficacy and reduce cumulative glucocorticoid doses, treatment regimens should be combined initially with three consecutive pulses of i.v. methylprednisolone 500–750 mg, followed by oral prednisone 0.5 mg/kg/day for 4 weeks, reducing to $\leqslant$ 10 mg/day by 4–6 months	98
4.4 In pure class V nephritis with nephrotic-range proteinuria, MPA (MMF target dose 3 g/day for 6 months) in combination with oral prednisone (0.5 mg/kg/day) may be used as initial treatment based on better efficacy/toxicity ratio. CYC or calcineurin inhibitors (ciclosporin, tacrolimus) or rituximab are recommended as alternative options or for non-responders.	95
4.5 AZA (2 mg/kg/day) may be considered as an alternative to MPA or CYC in selected patients without adverse prognostic factors (as defined 4.2), or when these drugs are contraindicated, not tolerated or unavailable. AZA use is associated with a higher flare risk.	96
Subsequent treatment	
4.6 In patients improving after initial treatment, subsequent immunosuppression is recommended with either MPA at lower doses (initial target MMF dose 2 g/day) or AZA (2 mg/kg/day) for at least 3 years, in combination with low-dose prednisone (5–7.5 mg/day). Gradual drug withdrawal, glucocorticoids first, can then be attempted.	97
4.7 Patients who responded to initial treatment with MPA should remain on MPA unless pregnancy is contemplated, in which case they should switch to AZA at least 3 months prior to conception.	98
4.8 Calcineurin inhibitors can be considered in pure class V nephritis.	93
Refractory disease	
4.9 For patients who fail treatment with MPA or CYC, either because of lack of effect (as defined above) or due to adverse events, we recommend that the treatment is switched from MPA to CYC, or CYC to MPA, or that rituximab be given.	95
5. **Adjunct treatment in patients with LN**	
5.1 Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are indicated for patients with proteinuria (UPCR >50 mg/mmol) or hypertension.	98
6. **Management of end-stage renal disease in LN**	
6.1 All methods of renal replacement treatment can be used in lupus patients, but there may be increased risk of infections in peritoneal dialysis patients still on immunosuppressive agents, and vascular access thrombosis in patients with aPLs.	98
6.2 Transplantation should be performed when lupus activity has been absent, or at a low level, for at least 3–6 months, with superior results obtained with living donor and pre-emptive transplantation. aPLs should be sought during transplant preparation because they are associated with an increased risk of vascular events in the transplanted kidney.	96
7. **APS-associated nephropathy in SLE**	
7.1 In patients with lupus and APS-associated nephropathy (APSN), HCQ and/or antiplatelet/anticoagulant treatment should be considered.	91

[a]Reproduced from Bertsias *et al.* Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 71: 771–82. Copyright 2012, with permission from BMJ Publishing Group Ltd [24]. Numbers are mean (S.D.) and median (IQR) agreement level among authors. A score of 10 represents the highest SOA. GFR: glomerular filtration rate; SOA: strength of agreement; UPCR: urine protein:creatinine ratio.

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detailed review by at least two members of the group. There was considerable overlap in the topics covered by the papers, which were reviewed by various members of the group.

Development of the guideline: levels of evidence and consensus agreement

The recommendations were developed in line with the BSR's Guidelines Protocol, using RCP, SIGN and AGREE II methodology to assess the level of evidence (LOE) and grade of recommendation (GOR). Papers selected for review and the evidence obtained from them were categorized by at least two members of the group, according to the study design, using the SIGN methodology (supplementary Table S2, available at *Rheumatology* Online), and the level of the evidence was graded by combining information on the design and validity of the available research studies to provide the GOR for each component of each statement. The results of the literature search were summarized, aggregated and distributed to the expert committee by three of us (C.G., M.G., M.A.), and the GOR for each item was ratified by the expert committee. Draft recommendations were discussed and rephrased at a face-to-face meeting and subsequently by email, following an updated literature review. The LOEs and the GORs for the data supporting the guideline recommendations are shown in Tables 1 and 2. Finally, the six recommendations for the management of SLE and the main items in the EULAR/ERA-EDTA recommendations for LN [24] (Table 3) were voted on by clinical members of the guideline development group. For each recommendation, the SOA of all clinical members of the group was sought on a scale of 1 (no agreement) to 10 (complete agreement); the mean percentage agreement was calculated and is shown after each recommendation (all >90% and supported by other members of the group). The guideline will be reviewed in 5 years' time.

The guideline

Eligibility criteria

This guideline is designed to cover the management of adult patients with SLE by healthcare professionals. These recommendations are based on the literature review covering the diagnosis, assessment, monitoring and treatment of mild, moderate and severe lupus, including neuropsychiatric (NP) disease. The focus of the literature review was on non-renal disease, as the EULAR/ERA-EDTA recommendations for LN (see below) were published [24] close to the time that we started work on this guideline.

Exclusion criteria

Management of paediatric lupus, renal lupus, topical treatment for cutaneous lupus, and drug treatment in pregnancy have been excluded from our literature search and guideline development. BSR guidelines on the use of drugs in pregnant patients with rheumatic diseases (including lupus) have been developed in parallel with this guideline.

Introduction to the recommendations and supporting evidence

For each question addressed by the literature review (supplementary data section Search strategy, available at *Rheumatology* Online), we provide first the recommendations and the overall LOE, GOR and SOA for each, followed by the rationale. The rationale consists of a summary of the evidence supporting the statements (including cautions in the case of drug therapy). It is organized by topic and includes some key points about the studies leading to the recommendations and a conclusion for each topic discussed. The number of studies and types of studies (with references) leading to the LOE and GOR are summarized in Table 1 for the items contributing to the recommendations on diagnosis, assessment and monitoring of lupus, and in Table 2 for those relating to the treatment and prevention of mild, moderate and severe non-renal lupus. In Table 3 we provide our SOA with key points of the EULAR/ERA-EDTA recommendations for the management of LN [24], so that the management of the most important aspects of lupus are covered by this guideline in a single document.

Recommendations for clinical and serological features prompting consideration of a diagnosis of SLE

(i) SLE is a multisystem autoimmune disorder. The diagnosis requires a combination of clinical features and the presence of at least one relevant immunological abnormality. If there is a clinical suspicion of lupus, blood tests (including serological marker tests) should be checked (LOE 2++, GOR B, SOA 98%).

(ii) ANAs are present in ~95% of SLE patients. If the test is negative, there is a low clinical probability of the patient having SLE. A positive ANA test occurs in ~5% of the adult population, and alone it has poor diagnostic value in the absence of clinical features of autoimmune rheumatic disease (2++/B, SOA 96%).

(iii) The presence of anti-dsDNA antibodies (2++/B), low complement levels (2+/C) or anti-Smith (Sm) antibodies (2+/C) are highly predictive of a diagnosis of SLE in patients with relevant clinical features. Anti-Ro/La and anti-RNP antibodies are less-specific markers of SLE (2+/C) as they are found in other autoimmune rheumatic disorders as well as SLE (2+/C) (SOA 95%).

(iv) aPLs should be tested in all lupus patients at baseline, especially in those with an adverse pregnancy history or arterial/venous thrombotic events (2++/B). Confirmatory tests for APS are positive LA, aCL (IgG, IgM) and/or anti-beta-2 glycoprotein-1

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(IgG, IgM) on two occasions at least 12 weeks apart (2 ++/B) (SOA 97%).

Rationale

Clinical manifestations

SLE is a multisystem autoimmune disease [1, 8] with considerable heterogeneity. This makes the diagnosis, assessment and monitoring a challenging process [10, 26–28, 41]. Delays in diagnosis are well recognized and remain a concern [242]. Some of the most typical features and their cumulative incidence are shown in supplementary Table S3, available at *Rheumatology* Online [7, 10, 26–29]. It is important to ensure that the diagnosis of lupus is appropriate before considering treatment [41, 243]. Given the variety of clinical manifestations that can occur, lupus should be considered in the differential diagnosis of many acute and sub-acute presentations, particularly, but not exclusively, in individuals at increased risk of the disease, such as women from African, South Asian or Chinese backgrounds [2, 244]. Lupus can also affect men, resulting in severe disease, including renal involvement and greater risk of damage compared with women in some but not all reports [15, 16, 30, 31].

Renal and neurological involvement are major causes for morbidity and mortality in SLE [2, 7, 15, 16, 32, 33]. Renal disease is clinically silent and must be actively sought to prevent renal damage as discussed below. A working party of the ACR distinguished 19 NP manifestations that may occur in SLE patients [245]. Not all are directly attributable to the SLE disease process, and the true incidence of these manifestations is hard to ascertain as most of them are uncommon [23, 246]. Gastrointestinal and hepatic features occur in 39–67% of patients [42, 247] and are often not recognized as being due to lupus. As with cardiorespiratory features, they must be distinguished carefully from infection, adverse events from drugs and co-morbid conditions. Ophthalmic manifestations of lupus are rare, but potentially sight-threatening, and need careful evaluation by an experienced ophthalmologist [248–250].

Serological (immunological) manifestations

The clinical features of acute lupus are mostly due to inflammatory processes triggered by the formation of immune complexes involving autoantibodies and complement consumption, although thrombosis associated with aPLs may contribute to the pathogenesis in some patients [1, 8, 10]. With a clinical suspicion of SLE, an initial autoantibody screen should be performed. Approximately 95% of lupus patients are ANA positive, and 98% of patients will have positive ANA and/or anti-dsDNA antibodies [26, 36, 37]. ANA tests, although sensitive, are not specific for the diagnosis of lupus, and ANAs can occur in a variety of other conditions, including SS, SSc, DM, viral infections (e.g. infectious mononucleosis) and malignancy [36, 41]. The ANA test can increase in titre over time or can become negative in treated patients, and the results can vary with different assays [34, 37].

If patients have a strong clinical likelihood of having lupus, anti-dsDNA antibody testing should be done [38]. Anti-dsDNA and anti-Sm antibodies are much more specific for lupus, being very rare in other conditions [36] but they are less sensitive than ANA (supplementary Table S3, available at *Rheumatology* Online) [10, 26–29, 251]. Both the Farr and the ELISA methods are acceptable for measuring anti-dsDNA antibodies, with the former yielding higher sensitivity and specificity rates [24, 39, 40]. The *Crithidia luciliae* immunofluorescence test also has a high specificity for SLE. Additional routine serological tests are the complement C3 and C4 levels [43]. C3 generally has a higher sensitivity than serum C4 for active LN, but both tests have modest specificity and their clinical utility lies in their high negative predictive value (>90%) to exclude active disease, especially renal disease [24, 44–46].

Anti-Ro (SSA), anti-La (SSB) and anti-RNP antibodies are less specific markers for the presence of SLE, as they are found in other autoimmune rheumatic disorders [41]. Anti-Ro and anti-La are most strongly associated with primary SS but do occur in lupus patients, especially those with photosensitivity and subacute cutaneous lupus. Anti-Ro and anti-La antibodies can cause neonatal lupus syndrome including congenital heart block (CHB) in children born to mothers with these antibodies (see Recommendations for monitoring of SLE section) [64, 65]. Anti-RNP antibodies are found in overlap conditions such as MCTD [41].

All lupus patients should be tested for aPLs because their presence indicates a group at increased risk of arterial/venous thrombotic events and adverse pregnancy outcomes [241, 252, 253]. As APS and SLE often overlap, and APS sometimes evolves in to SLE, the presence of APS should also prompt assessment for lupus. Confirmatory tests for APS are positive LA, aCL (IgG, IgM), and/or anti-beta-2 glycoprotein-1(IgG, IgM) antibodies on two occasions at least 12 weeks apart [241, 252]. The LA test is the most specific of the three tests and is associated with a higher positive predictive value. The most high-risk aPL profile (triple positivity including positive LA, aCL and anti-β2-glycoprotein-I antibody) is associated with a cumulative incidence of thrombosis after 10 years of 37.1% [254].

Classification criteria for lupus

Based on the ACR (previously the American Rheumatism Association) revised criteria for SLE published in 1982 [255] and the 1997 modification [256], a patient may be classified as having SLE if they have 4 or more of 11 criteria present (Table 4). However, not all patients who meet these criteria have lupus, and not all patients diagnosed clinically with lupus have four or more of these criteria, which may appear or disappear over time [7, 33, 35, 257]. There has been a tendency to consider patients who meet the ACR classification criteria for lupus to have the disease, even if they only have certain clinical features without evidence of one or more of the immunological abnormalities that are the hallmark of this autoimmune

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Table 4 The ACR criteria for classification of SLE[a]

Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
Serositis	Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR Pericarditis: documented by ECG or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria >0.5 g/day or $>3+$ if quantitation not performed OR Cellular casts: may be red cell, haemoglobin, granular, tubular or mixed
Neurologic disorder	Seizures: in the absence of offending drugs or known metabolic derangements; e.g. uremia, ketoacidosis or electrolyte imbalance OR Psychosis: in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance
Haematologic disorder	Haemolytic anaemia with reticulocytosis OR Leukopenia $<4000/mm^3$ total on two or more occasions OR Lymphopenia $<1500/mm^3$ on two or more occasions OR Thrombocytopenia $<100\,000/mm^3$ in the absence of offending drugs
Immunologic disorder	Anti-DNA: antibody to native DNA in abnormal titre OR Anti-Sm: presence of antibody to Sm nuclear antigen OR Positive finding of aPLs on: an abnormal serum level of IgG or IgM aCL; a positive test result for LA using a standard method, or; a false positive test result for at least 6 months confirmed by *Treponema pallidum* immobilization or the fluorescent treponemal antibody absorption test
ANA	An abnormal titre of ANA by immunofluorescence, or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

[a]The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation. Adapted from Tan EM *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271–7, copyright 1982 [255]; and Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725, copyright 1997 [256], with permission from John Wiley & Sons. Anti-Sm: anti-Smith antibody.

disease. Conversely, sometimes the disease has been diagnosed on the basis of auto-antibodies and haematological features, without consideration of whether the whole clinical and serological picture is consistent with lupus being the most likely diagnosis.

To address these and some other issues, the SLICC group devised alternative classification criteria for lupus [258]. These criteria introduced a requirement for at least one clinical and one immunological criterion and two others from an expanded list of items (Table 5) compared with the ACR criteria (Table 4) [256]. They also allowed biopsy-proven LN in the presence of ANA or anti-dsDNA antibodies to be classified as lupus, without the need for other criteria [258]. The serological criteria include low complement (C3 and/or C4), as this item reflects complement consumption due to the formation of immune complexes in active lupus disease.

These revised SLICC lupus criteria have been accepted by the European Medicines Agency, the US Food and Drug Administration and NHS England as being suitable for the inclusion of patients in clinical trials and in the commissioning policy for rituximab. They are more intuitive than the previous ACR classification criteria when considering a diagnosis of lupus, and allow a larger number of patients to meet criteria; however, diagnosis should not be restricted to patients who meet the classification criteria, as they can encompass other manifestations in the appropriate serological context [259]. The SLICC criteria have been tested in a number of cohorts and in most studies have shown an increase in sensitivity and reduced specificity, so care is needed if features are better explained by an alternative diagnosis [260–263].

Conclusions

When considering a patient with a possible diagnosis of lupus, a detailed clinical history and examination is required in order to identify relevant clinical features, including assessment of haematological and renal parameters. The diagnosis should not be made without evidence of at least one autoantibody or low complement levels to support the diagnosis of this autoimmune disease, consistent with the SLICC classification criteria. The ACR (Table 4) and SLICC (Table 5) classification criteria are not diagnostic criteria but may be helpful when considering the diagnosis;

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Table 5 Clinical and Immunologic Criteria Used in the SLICC Classification Criteria for SLE[a]

Clinical Criteria
Acute cutaneous lupus including:
lupus malar rash (do not count if malar discoid), bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, (in the absence of dermatomyositis), or subacute cutaneous lupus, nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
Chronic cutaneous lupus including:
classical discoid rash, localized (above the neck), generalized (above and below the neck), hypertrophic, (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap
Oral ulcers:
Palate, buccal, tongue, or nasal ulcers (in the absence of other causes, such as vasculitis, Behcet's disease, infection (herpes viruses), inflammatory bowel disease, reactive arthritis, acidic foods)
Nonscarring alopecia:
diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia)
Synovitis involving two or more joints:
characterized by swelling or effusion or tenderness in 2 or more joints and thirty minutes or more of morning stiffness.
Serositis:
typical pleurisy for $>$ 1 day or pleural effusions or pleural rub or typical pericardial pain (pain with recumbency improved by sitting forward) for $>$ 1 day or pericardial effusion or pericardial rub or pericarditis by EKG (in the absence of other causes, such as infection, uremia, and Dressler's pericarditis)
Renal:
Urine protein:creatinine ratio (or 24 hr urine protein) representing 500 mg of protein/24 hr or red blood cell casts
Neurologic:
seizures, psychosis, mononeuritis multiplex (in the absence of other known causes such as primary vasculitis), myelitis, peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus), acute confusional state (in the absence of other causes, including toxic-metabolic, uremia, drugs)
Hemolytic anemia
Leukopenia: $<$ 4000/mm^3 at least once (in the absence of other known causes such as Felty's, drugs, portal hypertension) OR
Lymphopenia: $<$ 1000/mm^3 at least once (in the absence of other known causes such as corticosteroids, drugs and infection)
Thrombocytopenia: $<$100,000/mm^3 at least once (in the absence of other known causes such as drugs, portal hypertension, TTP)
Immunologic Criteria
ANA level above laboratory reference range
Anti-dsDNA antibody level above laboratory reference range (or $>$ 2 fold the laboratory reference range if tested by ELISA)
Anti-Sm
Antiphospholipid antibody:
any of the following: lupus anticoagulant, false-positive rapid plasma regain (RPR), medium or high titer, nticardiolipin antibody level (IgG, IgM or IgA), anti-β_2 glycoprotein I (IgG, IgM or IgA)
Low complement:
low C3, low C4, low CH50
Direct Coombs' test (in the absence of hemolytic anemia)

[a]Patients can be classified as having SLE if they satisfy four of the clinical and immunological criteria, including at least one clinical criterion and one immunologic criterion, OR if they have biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies. Reproduced from Petri M *et al.* Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 64:2677–86. Copyright 2012. With permission from John Wiley & Sons [258]. TTP: thrombocytopaenic purpura; anti-Sm: anti-Smith antibodies.

however, they do not cover all the clinical manifestations of lupus. The LOEs and GORs for parameters supporting the diagnosis of lupus are shown in Table 1.

Recommendations for the assessment of SLE patients

(i) Clinical manifestations in SLE patients may be due to disease activity, damage, drug toxicity or the presence of co-morbidity. In the case of disease activity, it is important to ascertain whether this is due to active inflammation or thrombosis, as this will define treatment strategies (LOE 2++, GOR B, SOA 97%).

(ii) Clinical assessment of a lupus patient should include a thorough history and review of systems, full clinical examination and monitoring of vital signs, urinalysis, laboratory tests, assessment of

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health status and quality of life, and measurement of disease activity and damage using standardized SLE assessment tools (2++/B). Imaging (4/D), renal (2++/B) and other biopsies (4/D) should be performed where indicated (SOA 100%).

(iii) Disease activity is categorized into mild, moderate and severe, with the occurrence of flares (2+/C). Mild disease activity is clinically stable lupus with no life-threatening organ involvement, mainly manifesting as arthritis, mucocutaneous lesions and mild pleuritis. Patients with moderate disease activity have more serious manifestations, and severe disease is defined as organ- or life-threatening (4/D) (SOA 93%).

Rationale

Assessment of lupus

A systematic approach should be taken because of the diversity and complexity of clinical and laboratory manifestations (supplementary Table S3, available at *Rheumatology* Online) [264–266]. Clinical manifestations may be due to one or any combination of the following: disease activity from active inflammation or thrombosis, acute drug toxicity, chronic damage due to the effects of the disease or its treatment (such as lung fibrosis or atherosclerosis), or co-morbidity (e.g. infection). It is important to take a detailed history and to perform a clinical examination, including vital signs and urinalysis, to establish the likely differential diagnoses and then to organize the relevant investigations as suggested in Table 6, depending on the circumstances. In addition, when assessing disease activity with a view to planning treatment, it is necessary to determine the circumstances that may have led to a lupus flare (such as exposure to sunlight, concurrent or recent infection, hormonal changes, or timing of previous disease-related therapeutic change) as this will guide further investigation, treatment change (including non-drug measures) and disease monitoring required thereafter.

Validated instruments for the assessment of lupus

The most reliable way of assessing disease activity is to use a defined instrument for this purpose that has been validated and is available with an appropriate glossary and scoring instructions [265, 266]. For example, the NHS England Interim Clinical Commissioning Policy Statement for rituximab in lupus published in 2013 [267] recommended the use of two lupus-specific disease activity indices: the BILAG index and the SLEDAI. For such purposes, the currently recommended revised versions are the BILAG-2004 index [268, 269] (for BILAG-2004 index data collection form, glossary and scoring see supplementary data, available at *Rheumatology* Online) and SLEDAI-2K [270] or the SELENA-SLEDAI [271, 272] (see supplementary data, available at *Rheumatology* Online, for SLEDAI-2K and SELENA-SLEDAI index data collection forms). Modifications have been made for use in pregnancy [273, 274]. For optimal performance, training in the use of these instruments is advised. It is essential that only manifestations/items due to SLE disease activity are recorded and that the data collection forms are used in conjunction with the appropriate glossary and scoring rules. There is one validated instrument for assessing damage, the SLICC/ACR Damage Index (SDI) [275]. It is recommended that patients' assessment of their disease be captured using health status or quality of life questionnaires such as the generic Short-form36 (SF-36), which has been validated for use in lupus patients [276], or a lupus-specific questionnaire such as the Lupus Quality of Life (LupusQoL) [277]. There is agreement that for best practice these instruments should be used [74, 278], although there are no data confirming that their use improves the outcomes for patients. Better outcomes are achieved if lupus in-patients are managed in centres with experience in managing lupus [279–282].

Definitions of mild, moderate and severe lupus

For the purpose of planning appropriate treatment, disease activity has been broadly categorized as mild, moderate or severe [8], and worsening disease activity is termed flare, which can be similarly categorized as mild, moderate or severe [283, 284]. Examples are shown in Table 7. The term mild disease activity reflects clinically stable disease with no life-threatening organ involvement and that is not likely to cause significant scarring or damage. Examples of scores for such patients when using formal assessment tools would include a SLEDAI-2K score of <6 [270] and/or one BILAG B score [269]. Patients with moderate disease have more serious manifestations, which if left untreated would cause significant chronic scarring. Examples of scores for such patients when using formal assessment tools would include a SLEDAI-2K score in the range of 6–12 [270] and/or two or more BILAG B scores [269]. Severe disease is defined as organ or life threatening and reflects the most serious form of systemic disease that requires potent immunosuppression. Examples of scores for such patients when using formal assessment tools would include a SLEDAI-2K score of >12 [270] and/or at least one BILAG A score [269].

Conclusions

The assessment of a patient with lupus, as with making the initial diagnosis, is dependent on a careful history and examination of the patient, with relevant haematological, biochemical and immunological testing as well as other investigations as necessary (shown in Table 6) to establish the degree of disease activity and accumulation of chronic damage, and to identify other complications or co-morbid conditions that will influence the treatment plan. The LOEs and GORs for the components of the assessment and monitoring of lupus disease are shown in Table 1.

Recommendations for monitoring of SLE

(i) Patients with lupus should be monitored on a regular basis for disease manifestations, drug toxicity and co-morbidities (LOE 2++, GOR B, SOA 99%).

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Table 6 Assessment and monitoring of SLE in lupus patients

Item	Initial assessment	Assessment (active disease) Patients with active disease should be reviewed at least every 1–3 months	Monitoring (stable disease) Patients with stable/low disease activity should be reviewed every 6–12 months	Pregnancy Pregnancy counselling and follow-up
History and examination				
Detailed history	X	focused history	focused history	obstetric history
Clinical examination	X	X	X[a]	X
Vital signs (Blood pressure, heart rate, weight)	X	X	X	X
Drug review including vaccination status	X	X	X	X
Bloods				
Full blood count	X	X	X	X
Other tests for anaemia	X[a]	X[a]	X[a]	X[a]
Renal function	X	X	X	X
Bone profile	X	X[a]	X[a]	X
Liver function tests	X	X[a]	X[a]	X
Creatine kinase	X	X[a]	X[a]	X[a]
CRP	X	X[a]	X[a]	X[a]
Vitamin D3	X	X[a]	Annually	X
Thyroid function	X	X[a]	X[a]	X
Immunology				
ANA	X	–	–	X[a]
Anti-dsDNA titre, C3/C4 level	X	X	X	X
aPL (LA, aCL, anti-beta2-glycoptroteinl)	X	X[a]	X[a]	Repeat if negative in the past
Anti-Ro/La, anti-RNP and anti-Sm antibodies	X	–	–	Repeat if negative in the past
Immunoglobulins	X	X[a]	Annually[a]	X[a]
Direct Coombs' test	X	X[a]	X[a]	X[a]
Urine				
Urinalysis (screen for proteinuria, haematuria, leucocyturia and nitrites to exclude infection)	X	X	X	X
Urine random protein:creatinine ratio Or 24-h urine collection for protein	X[a]	X[a]	X[a]	X[a]
Urine microscopy (and culture)	X[a]	X[a]	X[a]	X[a]
Other investigations				
Microbiology (other)	X[a]	X[a]	X[a]	X[a]
Biopsy (e.g. skin, kidney)	X[a]	X[a]	X[a]	X[b]
Lung function tests	X[a]	X[a]	X[a]	X[a]
Neurophysiology	X[a]	X[a]	X[a]	X[a]
ECG	X	X[a]	X[a]	X[a]
Imaging				
Chest X-ray	X	X[a]	X[a]	X[b]
Other imaging (US, CT, MRI)	X[a]	X[a]	X[a]	X[b]
Modifiable cardiovascular risk factors				
Hypertension	X	X[a]	Annually	X
Dyslipidaemia	X	X[a]	Annually	X[a]
Diabetes mellitus	X	X[a]	Annually	X
High BMI	X	X[a]	Annually	X
Smoking	X	X[a]	Annually	X
Disease activity and damage scores				
BILAG (BILAG 2004 index) or	X	X[a]	Annually	BILAG2004P[c]
SLEDAI (SLEDAI-2K or SELENA SLEDAI)	X	X[a]	Annually	SLEPDAI[d]
SLICC/ACR Damage Index	X	X[a]	Annually	X
Quality of life questionnaires				
Short-form 36 or LupusQoL	X	X[a]	Annually	X[a]

[a]When indicated; [b]when indicated and benefit > risks; [c]BILAG2004 pregnancy version; [d]SLEDAI pregnancy version. Anti-Sm antibodies: anti-Smith antibodies.

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Table 7 SLE treatment strategies for examples of mild, moderate and severe lupus

Item	Mild activity/flare BILAG C scores or single B score; SLEDAI <6	Moderate activity/flare BILAG 2 or more systems with B scores, SLEDAI 6–12	Severe activity/flare (non-renal) BILAG 1 or more A scores; SLEDAI >12
Typical manifestations attributed to lupus	Fatigue, malar rash, diffuse alopecia, mouth ulcers, arthralgia, myalgia, platelets 50–149 $\times$ 10^9/l	Fever, lupus-related rash up to 2/9 body surface area, cutaneous vasculitis, alopecia with scalp inflammation, arthritis, pleurisy, pericarditis, hepatitis, platelets 25–49 $\times$ 10^9/l	Rash involving >2/9 body surface area, myositis, severe pleurisy and/or pericarditis with effusion, ascites, enteritis, myelopathy, psychosis, acute confusion, optic neuritis, platelets <25 $\times$ 10^9/l
Initial typical drugs and target doses if no contraindications	CSs[a]: topical preferred or oral prednisolone $\leqslant$20 mg daily for 1–2 weeks or I.m. or IA methyl-prednisolone 80–120 mg and HCQ $\leqslant$6.5 mg/kg/day and/or MTX 7.5–15 mg/week and/or NSAIDs (for days to few weeks only)	Prednisolone[a] $\leqslant$0.5 mg/day or i.v. methyl- prednisolone $\leqslant$250 mg $\times$ 1–3 or i.m. methyl-prednisolone 80–120 mg and AZA 1.5–2.0 mg/kg/day or MTX 10–25 mg/week or MMF 2–3 g/day or ciclosporin $\leqslant$2.0 mg/kg/day and HCQ $\leqslant$6.5 mg/kg/day	Prednisolone[a] $\leqslant$0.5 mg/day and/or i.v. methyl-prednisolone 500 mg $\times$ 1–3 or prednisolone $\leqslant$0.75–1 mg/kg/day and AZA 2–3 mg/kg/day or MMF 2–3 g/day or CYC i.v. or ciclosporin $\leqslant$2.5 mg/kg/day and HCQ $\leqslant$6.5mg/kg/day
Aiming for typical maintenance drugs/doses providing no contraindications	Prednisolone[a] $\leqslant$ 7.5 mg/day and HCQ 200 mg/day and/or MTX 10 mg/week	Prednisolone[a] $\leqslant$7.5 mg/day and AZA 50–100 mg/day or MTX 10 mg/week or MMF 1 g/day or ciclosporin 50–100 mg/day and HCQ 200 mg/day;	Prednisolone[a] $\leqslant$7.5 mg/day and MMF 1.0–1.5 g/day or AZA 50–100 mg/day or ciclosporin 50–100 mg/day and HCQ 200 mg/day;
	Aim to reduce and stop drugs except HCQ eventually when in stable remission	Aim to reduce and stop drugs except HCQ eventually when in stable remission	Aim to reduce and stop drugs except HCQ eventually when in stable remission

[a]The lowest effective dose of prednisolone or other CSs should be used at all times.

(ii) Those with active disease should be reviewed at least every 1–3 months (2+, C/D), with blood pressure (1+/A), urinalysis (1+/A), renal function (1+/A), anti-dsDNA antibodies (2++/B), complement levels (2+/C), CRP (2+/C), full blood count (3/C), and liver function tests (4/D) forming part of the assessment, and further tests as necessary (4/D). Patients with stable low disease activity or in remission can be reviewed less frequently, for example, 6–12 monthly (4/D) (SOA 99%).

(iii) The presence of aPLs is associated with thrombotic events, damage, and adverse outcomes in pregnancy (2++/B). If previously negative, they should be re-evaluated prior to pregnancy or surgery, or in the presence of a new severe manifestation or vascular event (4/D) (SOA 96%).

(iv) Anti-Ro and anti-La antibodies are associated with neonatal lupus (including CHB) and should be checked prior to pregnancy (1+/A) (SOA 100%).

(v) Patients with lupus are at increased risk of comorbidities, such as atherosclerotic disease, osteoporosis, avascular necrosis, malignancy and infection (2+/C). Management of modifiable risk factors, including hypertension, dyslipidaemia, diabetes, high BMI and smoking, should be reviewed at baseline and at least annually (4/D) (SOA 98%).

(vi) Immunosuppressive therapy may lead to toxicities. Close monitoring of drugs by regular laboratory tests and clinical assessment should be performed in accordance with drug monitoring guidelines (4/D) (SOA 98%).

Rationale

Frequency of monitoring lupus/follow-up visits

There are no randomized controlled trials (RCTs) comparing different monitoring strategies in terms of frequency and details of assessments performed; however, data from various cohort studies have informed our expert opinion and previous guidelines in this respect [22, 71, 74, 278]. Patients should be told to report to clinicians if they develop any new or significant worsening of clinical manifestations. In most patients with active clinical disease, clinic visits should be approximately every 4 weeks initially, reducing gradually down to about 3-monthly reviews as the disease comes under control. There remains a significant risk of flare and the development of damage, even for patients who achieve early remission [72]. For most patients with mild features, including those who are clinically quiet but serologically active, 3-monthly visits are adequate [77]. Review should become more frequent if the disease becomes more active, especially if there is renal involvement,

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as the patients will require clinical, renal and serological evaluation (see below) [285]. For patients with inactive disease, without previous renal involvement or organ damage (that can predict increased risk of further active disease and damage), review may be less frequent, for example every 6 months providing treatment is stable and suitable drug monitoring is in place [74]. Patients should be seen more regularly, however, if treatment is being withdrawn or has been stopped, due to the risk of disease flare, even if they appear to be in remission [72].

Reasons for clinical monitoring in lupus patients

Regular monitoring of clinical and laboratory features of active disease should take place, with additional investigations as necessary (Table 6), to assess and monitor changes in disease activity, the development of chronic damage, and to detect the presence of (and changes in) co-morbid conditions that may be confused with lupus (such as FM, hypothyroidism, iron deficiency anaemia, infection), and drug-induced conditions [22, 74, 265]. LOEs for the laboratory parameters are shown in Table 1. Proteinuria (and renal function in particular [24]), high DAS [16, 48, 73, 286], new and different types of cutaneous lesions [50], arthritis [72], NP disease [16, 51] and cytopenias [52, 53] have been shown to correlate with disease severity and can predict future flares and the development of damage [11, 32, 49, 54, 55]. Only measurement of proteinuria and renal function have been shown to have strong predictive value for outcome [22, 24, 56]. Chest X-ray, ECG and other specific tests such as lung function, echocardiography and neurophysiology should be repeated during the course of the disease as necessary. When major organs are involved, additional imaging (such as brain MRI) and pathology (renal/skin biopsy) can add significant prognostic information, particularly renal biopsy, and may need to be repeated to assess response to treatment [22–24, 287, 288].

Interpretation of haematological, renal and other biochemical parameters

Lymphopenia is a common manifestation of lupus (supplementary Table S3, available at *Rheumatology* Online), and some patients will have leucopenia and neutropenia regularly with active disease [53]. This needs to be remembered when monitoring patients on cytotoxic therapy, as a fall in cell counts may signify the need to increase therapy for lupus rather than reduce or discontinue therapy if drug toxicity is suspected. It also means that the usual drug-monitoring limits of tolerance may need to be reviewed and personalized in the context of an individual with SLE. Thrombocytopenia may be acute and indicative of a disease flare, or low grade and chronic as part of of lupus and/or associated with APS [57].

ESR is often raised in active SLE [70], but can also reflect persistent polyclonal hypergammaglobulinaemia, and is not a reliable marker of disease activity. CRP is usually normal [66–68] or slightly elevated in the presence of serositis or arthritis [69]. A significantly raised CRP is more likely to indicate infection, and patients with raised CRP will need therefore to be thoroughly screened for infection, given that infection is the commonest cause of death in lupus patients. In contrast, a raised ESR does not discriminate between active lupus and infection [69]. Immune complexes of CRP and anti-CRP antibodies may form in lupus patients, possibly explaining the low levels of CRP observed with active disease [67].

Proteinuria should be quantified using the urine protein:creatinine ratio or 24-h urine collection. Microscopic examination of the urine to look for red cells and red cell casts is useful for identifying active renal disease and renal flares, but the assessment of casts is now rarely done [24, 289, 290]. When assessing haematuria, it is important to exclude infection, menstrual blood loss and calculi. White cells in the urine are most often due to urine or vaginal infection and can be hard to interpret, but as an otherwise unexplained finding, are associated with active tubulointerstitial inflammation.

Serum immunoglobulins should be measured prior to starting drugs such as MMF, CYC and rituximab which have the most risk of inducing immunoglobulin deficiency that might increase the risk of infection. The initial repeat measurement of the serum immunoglobulins should take place about 3–6 months later and can then be spaced out to annual checks [74, 199, 291, 292, 293]. Specific antibodies, for example, pneumococcal antibodies, may be assessed (if tests are available) to assess the need for and response to immunization. Screening for chronic infections (such as TB, hepatitis B and C, HIV, HPV) is recommended before starting immunosuppressants and repeated if reactivation of infection is suspected.

It is important to measure creatinine kinase at baseline and to continue to follow it in patients with myositis or myalgias that might be due to lupus or statins used to prevent atherosclerosis [75]. Monitoring of cholesterol and of other lipids, and remaining vigilant for and treating the development of diabetes mellitus and features of the metabolic syndrome (which may increase cardiovascular risk, particularly in patients on glucocorticoids), are important and should be as successful as in the general population [71, 74, 76]. Additional monitoring investigations should include Vitamin D3, which is often low as a consequence of sun avoidance and/or chronic kidney disease [294]. Vitamin D is required for optimal bone health, especially in patients on chronic glucocorticoid therapy and/or following the menopause [295]. Clinicians should have a low threshold for assessing thyroid function, as hypothyroidism can present with similar features to lupus; it co-exists with lupus in ~7% of patients, and thyroid antibodies are found in 14% [296–298].

Monitoring of lupus autoantibodies and complement

Serial anti-dsDNA antibodies and C3 and C4 levels are useful because rising, high anti-dsDNA antibodies and falling, low complement levels are associated with flare [49, 58], particularly in patients with LN [24]. In general, concomitantly rising anti-dsDNA titres [39, 43, 46, 49, 59, 60] and decreasing C3 and/or C4 levels [43–46] are more important predictors of current or impending flares than the absolute levels, and levels of anti-dsDNA antibodies may actually fall at the time of flare [299].

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It can be helpful to combine a sensitive but less specific anti-dsDNA antibody assay (e.g. ELISA) with one that only measures more specific, high affinity or high avidity antibodies (such as Farr radioimmunoassay or the *Crithidia* test), because only tests measuring high affinity and high avidity antibodies are strongly associated with renal disease; however, other ELISAs can be used to monitor disease activity [40]. Stable active serology without clinical features does not necessarily warrant therapy [71], but patients need to be followed closely, with individual care decisions made to prevent over- or undertreatment. Many physicians would avoid reducing therapy in this situation as patients may develop renal disease [300], but the serological tests do not always predict flare [61, 62, 71]. About 40% of lupus patients do not have anti-dsDNA antibodies, so for this group of patients, they are not useful for monitoring disease activity [63]. Some patients are heterozygous for the C4 allele and due to a null allele have a persistently low C4 level (at about 50% of normal), without having active disease, but C4 levels can still fluctuate with disease activity.

ANA, anti-Sm and anti-RNP antibodies tests should be carried out at baseline and do not need to be repeated at each visit, as levels do not fluctuate with disease activity. Anti-Ro and anti-La antibodies should be measured in women planning pregnancy or in early pregnancy, as they may be transferred across the placenta and are associated with CHB in ~1–2% of babies [64, 65]. Fetal heart-rate monitoring should be instituted from week 16 of pregnancy and continued throughout pregnancy in women with either of these antibodies. Neonatal lupus rash develops in ~10% of babies born to mothers with these antibodies (especially if exposed to UV light), and laboratory abnormalities (cytopenias and abnormal liver function tests) have also been observed in babies exposed to these antibodies [64].

aPLs should be assessed at baseline and, if previously negative, they should be re-evaluated in the presence of a new vascular event, adverse pregnancy outcome or other new manifestation that might have a thrombotic component, as well as prior to a planned pregnancy [47, 241, 252, 253]. Positive tests for APS include LA, aCL (IgG, IgM) and/or anti-beta-2 glycoprotein 1(IgG, IgM), and these tests should be repeated after 12 weeks to confirm positivity [241, 252], although LA cannot be evaluated if anticoagulation has been started, as this would interfere with the assay.

Monitoring for the development of co-morbidities

Patients with lupus are at increased risk of co-morbidities [71, 74], such as infection, premature cardiovascular and peripheral vascular disease, osteoporosis, avascular necrosis and some malignancies (non-Hodgkin's lymphoma, cervical, vulval, lung and thyroid cancer [301, 302]). The management of these issues is beyond the scope of this guideline and should follow national/international guidelines for each condition and include appropriate vaccinations [22, 71, 74, 278]. Nevertheless, screening for and managing these conditions is an integral part of the assessment and regular monitoring of lupus patients, as described in the EULAR recommendations for monitoring patients with SLE in clinical practice and in observational studies [74]. A preventative approach should be adopted, since the commonest causes of death in lupus patients in the UK are infection and cardiovascular disease, followed by malignancy [15, 16, 18]. Modifiable risk factors for co-morbidities to address include vaccination status, hypertension, dyslipidaemia, diabetes, high BMI and smoking. These should be reviewed at baseline and at least annually thereafter [22, 24, 71, 74]. These co-morbidities may occur at a younger age than in the normal population, and clinicians should screen regularly for them, even though there are no RCTs to suggest that more intense screening than that applied in the general population improves outcome in lupus patients [22, 24, 71, 74]. Routine cancer screening (particularly for cervical cancer, given the increased risk of HPV infection in lupus patients [303]) should not be forgotten due to emphasis on lupus disease management [304].

Monitoring of drugs

This should be similar to that for drugs used in other rheumatic diseases, but due to the occurrence of cytopenias and abnormal renal and liver function possibly caused by lupus disease itself, monitoring tests may need to be undertaken more frequently, and the interpretation of laboratory results is more difficult. Adherence to drugs may be confirmed by measuring drug levels (e.g. of ciclosporin, tacrolimus, mycophenolate [171] and HCQ [80]), but these tests are not widely available (except that for tacrolimus, which is tested in order to guide optimal dosing and to prevent renal toxicity). There is little lupus-specific data about target drug levels, and detailed discussion is beyond the scope of these recommendations, but this topic has been reviewed for rheumatic diseases in general [78] as well as for lupus [305]. It should be noted that, like other chronic conditions, adherence levels are suboptimal in lupus, and therefore specific consideration of this issue is needed in patients showing poor response to therapy [79].

Conclusions

It is important to monitor lupus patients regularly to assess and monitor changes in disease activity, chronic damage, and in drug-induced and co-morbid conditions that may be confused with lupus and that are associated with an increased risk of death. The LOEs and GORs for the main components of monitoring of lupus patients are shown together in Table 1, and a suggested protocol is shown in Table 6.

Recommendations for the management of mild SLE

(i) Treatments to be considered for the management of mild non-organ-threatening disease include the disease-modifying drugs HCQ (1++/A) and MTX (1+/A), and short courses of NSAIDs (3/D) for symptomatic control. These drugs allow for the avoidance of or dose reduction of CSs (SOA 94%).

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(ii) Prednisolone treatment at a low dose of $\leqslant$7.5 mg/day may be required for maintenance therapy (2+/C). Topical preparations may be used for cutaneous manifestations, and IA injections for arthritis (4/D) (SOA 93%).
(iii) High–Sun Protection Factor (SPF) UV-A and UV-B sunscreen are important in the management and prevention of UV radiation–induced skin lesions (2++/B). Patients must also be advised about sun avoidance and the use of protective clothing (4/D) (SOA 97%).

Rationale

Overview of treatment of mild lupus

Mild lupus features (Table 7) are distressing for patients and warrant treatment to relieve symptoms and signs. Such treatment may prevent progression to severe manifestations requiring more intense immunosuppression. These manifestations can be managed with CSs, HCQ and other antimalarials, MTX, NSAIDs and sunscreens. The LOEs and GORs for the drugs used to treat lupus disease are summarized in Table 2, and the SOAs with the recommendations are above. There are little data to support the use of topical therapies, dapsone, retinoids, thalidomide or danazol in the treatment of refractory cutaneous lupus rashes and vasculitis, and as these drugs are not used for other systemic features of lupus, they are not discussed here but have been reviewed [287, 288].

CSs for mild lupus

Summary

Topical preparations should be used initially for cutaneous manifestations, and intra-articular (IA) or intramuscular (i.m.) injections of CSs for arthritis. Short courses of oral prednisolone (up to 20 mg/day) are used for short periods of time (up to 14 days and reduced rapidly) to induce remission in some cases of mild lupus where local treatment is not sufficient or practical (evidence discussed below in moderate lupus). Prednisolone can be used in women who are trying to conceive, are pregnant or are breast-feeding [239].

Evidence

There are no RCTs comparing different types of CS administration, such as skin creams and ointments, intralesional, IA and i.m. injections, and oral CS drugs (usually prednisolone in the UK). CSs contribute to the development of chronic damage and co-morbidities such as cataracts, osteoporotic fractures, diabetes, atherosclerosis and infection [12, 14]. It has been shown that a 1 mg/day increase in maintenance prednisone dose is associated with a 2.8% increase in the risk of new organ damage, and that prednisolone dosing of $\leqslant$7.5 mg/day is associated with less risk of cataracts, osteoporotic fractures and cardiovascular damage than higher doses [306].

Conclusions

The lowest possible dose/amount of CSs should be used due to their side effects, including the risk of contributing to chronic damage and infection. Prednisolone treatment at a low dose of $\leqslant$7.5 mg/day may be required for maintenance therapy and has less risk of side effects than higher doses (2+/C).

HCQ and other anti-malarial agents

Summary

There is good evidence (Table 2) for the efficacy and safety of HCQ, the most commonly prescribed anti-malarial agent and one of the few licensed drugs for lupus. Providing that the patient has normal renal and liver function, HCQ can be used at doses of up to 6.5 mg/kg/day and is compatible with pregnancy and breast-feeding. It is used (Table 7) for skin and joint involvement, myalgia, fever, fatigue, pleurisy, to reduce the development of renal disease and chronic damage [14, 121] and for its steroid-sparing properties (even in patients with more severe disease) [71]. Chloroquine is used if HCQ is not available or not tolerated; however, there is less evidence for benefit and it has a greater risk of retinal toxicity than HCQ [121]. Mepacrine (quinacrine) is used predominantly for cutaneous lupus and has the least risk of ocular toxicity [287, 307–309].

Evidence

The benefits of anti-malarials on lupus activity were reported in four RCTs [81–84], five prospective cohort studies [87–91], three retrospective cohort studies [92–94] and an open-label extension of the first RCT [95]. There have been two other double-blind RCTs confirming that lupus rashes significantly improve with HCQ [85] and chloroquine [86]. The cohort studies have shown that response often takes 3–4 months [94], but at 6 months only 60% of patients with discoid rash show some response [94]. Another study showed that 20% of patients with an adequate response lose it within 2 years and need other therapies [310]. Higher drug levels were associated with increased cutaneous response in a prospective study [311]. In a double-blind RCT [80], low drug levels were associated with increased disease activity. Systemic features and smoking are also associated with an increased risk of poor response [94, 96, 122].

Many of the studies showing increased flare rates in patients who discontinued HCQ involved pregnant patients. A RCT in lupus patients [84] and two prospective [87, 90] cohort studies support the use of this drug before conception and in pregnancy to reduce flares in the mother. Although HCQ can cross the placenta, exposure is not associated with significant adverse effects on the fetus [87, 90, 97–100]. HCQ has anti-thrombotic as well as anti-inflammatory properties and by reducing disease activity in the mother may improve the outcome for the child by improving placental function [101, 102]. There is increasing evidence that HCQ reduces the risk of CHB in babies born to mothers with anti-Ro antibodies [103, 312, 313]. Further evidence supporting the use of HCQ in pregnant women as well as in those planning pregnancy and breast-feeding is reviewed in the BSR Guidelines on drugs in pregnancy in the rheumatic diseases [239].

There is further evidence from high-quality prospective and retrospective cohort studies that patients treated with anti-malarials (particularly HCQ) not only have lower levels

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of overall lupus activity and reduced rates of flare [80, 81, 84, 89, 90, 95], but can be managed with lower doses of CSs [83, 84, 90, 104]. The patients are more likely to stay clinically quiescent if HCQ is continued when the disease goes in to remission [105]. Patients on MMF are more likely to achieve renal remission if treated with HCQ [93]. Patients on HCQ are less likely to develop serious renal disease and have delayed time to renal damage [104], lower frequency of seizures [106] and less NP damage [107], greater delay in integument damage [108], less overall damage [109, 110] and, most importantly, improved survival [111, 112]. Some of the benefits on survival may be mediated by the beneficial effects of anti-malarials on total cholesterol, LDL-cholesterol, triglycerides, glucose [113] and/or by the prevention of thrombosis [101, 102, 121] and atherosclerotic plaque formation [114].

Patients take HCQ on average for about 6 years [115–118]. In general HCQ is well tolerated and better tolerated than chloroquine [86, 115, 116, 121]. The commonest adverse effects of anti-malarials are gastrointestinal, but a few patients stop because of headache, dizziness, itching, rash, non-retinal eye problems, hearing loss, myopathy or other rare neuromuscular side effects [121, 287]. The most serious adverse events are cardiac (which are very rare) [119] and retinopathy (which is more common with chloroquine than HCQ) [121, 314]. Retinopathy is unpredictable but unlikely with <7 years treatment with HCQ. It is more common thereafter [120] and with doses of HCQ above 6.5 mg/kg/day, or renal or liver impairment. It requires active screening to detect it early when it is asymptomatic and is most likely to be reversible [120, 314]. Policies on screening for ocular toxicity vary between countries and local guidelines should be followed [314, 315]. In general in the UK, baseline and yearly optician eye tests are recommended initially, with more detailed ophthalmological screening after 5 years of therapy [316].

Conclusions

There are good data from two systematic reviews and a meta-analysis including 7 RCTs and 36 cohort studies supporting the use of HCQ in lupus patients to reduce disease activity and as a steroid-sparing agent: overall LOE 1++, GOR A. HCQ should be given to all patients with mild lupus to prevent flares, the development of damage and to improve survival. It is recommended that HCQ be continued or started, even in those developing disease severe enough to warrant immunosuppressive therapies, including LN [22, 24, 25]. However patients with renal or liver dysfunction should have the dose reduced [314]. It is compatible with conception, pregnancy and breast-feeding. Unfortunately, it has a long half-life and takes at least 2 months to be effective [287, 309]. Patients need to be warned about this or they may discontinue the drug prematurely.

MTX in mild SLE

Summary

Although not licensed for the treatment of lupus, low-dose weekly MTX ($\leqslant$25 mg/week) has been used to reduce mild and moderate disease activity in lupus, particularly to control inflammatory arthritis and lupus skin rashes, originally on the basis of a variety of case series and cohort studies [317, 318]. MTX was originally used in patients who had failed HCQ and low-dose CSs, but it can be used with HCQ to avoid CSs or to promote CS dose reduction. Caution has been advised on the use of MTX in patients with LN, particularly as those with renal impairment will be at increased risk of MTX toxicity [317]. It is contra-indicated in women trying to conceive or pregnant as it is teratogenic. For these patients AZA would be more suitable (see section on moderate lupus for evidence).

Evidence

A systematic review by Sakthiswary and Suresh [319] summarizes the data from three controlled trials (two double-blind, placebo-controlled trials [123, 124], and a controlled open-label trial comparing MTX and chloroquine [125]) and five observational studies (two open-label prospective studies [126, 127]; a cross-sectional study [128]; a retrospective case–control cohort study [129]; and an open-label controlled study [130]). Another systematic review [133] includes two additional case series [131, 132]. These studies support the use of MTX to reduce mild and moderate lupus disease activity, and some demonstrated steroid-sparing properties. Some of these studies showed benefit specifically in treating lupus arthritis, rashes, vasculitis, serositis, myositis and constitutional symptoms, but there was little change in ESR, anti-dsDNA antibodies, C3 or C4 levels, except in a study with longer duration than previous studies [130]. The reduction in SLEDAI in the five controlled studies reporting these data included in the systematic review [319] was calculated to have an odds ratio = 0.444 (95% CI: 0.279, 0.707; $P = 0.001$). The analysis of the four controlled studies reporting steroid-sparing properties for MTX provided an odds ratio = 0.335 (95% CI: 0.202, 0.558; $P = 0.001$). Side effects led to discontinuation in $\sim$10% of patients but were not serious. It is teratogenic and should not be used in women within 3 months of planning to conceive, or who are pregnant or breast-feeding [239], nor in patients with renal impairment, because reduced renal function increases the risk of adverse events, particularly bone marrow suppression.

Conclusions

There are good data from two systematic reviews including three RCTs and seven cohort studies supporting the use of MTX in lupus to reduce disease activity and as a steroid-sparing agent: overall LOE 1+, GOR A.

NSAIDs in mild SLE

Summary

There are no RCTs of NSAIDs in SLE. Publications support the cautious use of NSAIDs for short periods of time for symptom control in SLE (inflammatory arthralgia, myalgia, chest pain and fever) where potential benefit outweighs the known risks of NSAIDs and paracetamol has been insufficient or not tolerated. The risk of NSAID-induced acute renal failure is increased in patients with LN, so NSAIDs

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should be avoided in patients with renal involvement. NSAID-induced allergic reactions, aseptic meningitis, cutaneous reactions and hepatotoxicity are increased in SLE patients. Caution is required in pregnancy [240].

Evidence

A review of the literature on non-selective Cox inhibitors and selective Cox-2 inhibitors [320] highlighted the potential increased risk of renal, hepatic and neurological toxicity in lupus patients. A retrospective case series assessing celecoxib, with a detailed literature review of NSAIDs [321] and a more comprehensive systematic review addressing the risk–benefit ratio of non-selective and selective inhibitors of cyclooxygenases in SLE patients, were published subsequently [134]. More recently it has become clear that NSAIDs (except possibly naproxen) can predispose to acute myocardial infarction in individuals with coronary heart disease [322], which is an additional reason for caution in lupus patients.

Conclusions

Based on one systematic review of the evidence from case series and case reports, the overall LOE for NSAIDs in non-renal mild lupus is three and GOR is D.

High-SPF UV-A and UV-B sunblock in SLE

Summary

There is clear evidence that ultraviolet radiation (UV-A and UV-B) can induce various forms of cutaneous lupus [287]. Patients with systemic lupus without cutaneous features have also been found to have an abnormal reaction to UV irradiation [323].

Evidence

Sunscreens were shown to prevent discoid and subacute cutaneous lupus rashes in a case series [141] and to reduce systemic features such as renal disease, thrombocytopenia and hospitalization in a cohort study [136]. Three open-label controlled trials [137–139], a retrospective case series [140] and a double-blind, controlled trial [135] have shown that sunscreens that block UV-A and UV-B can reduce UV radiation–induced lesions of cutaneous lupus.

Conclusions

Lupus patients should be advised about avoidance of sun and other sources of UV irradiation, and about the use of sunscreens (UV-A protection five stars and UV-B protection from SPF factors 30 to 50 products, which can be prescribed on the NHS) and protective clothing. Overall, the LOE is 2++ for sunscreens (one small RCT and six other studies) in lupus patients to prevent cutaneous lesions, and the GOR is B.

Recommendations for the management of moderate SLE

(i) The management of moderate SLE involves higher doses of prednisolone (up to 0.5 mg/kg/day) (2+/C), or the use of i.m. (4/D) or i.v. doses of methylprednisolone (MP) (2+/C). Immunosuppressive agents are often required to control active disease and are steroid-sparing agents (2+/C). They can also reduce the risk of long-term damage accrual (4/D) (SOA 98%).

(ii) MTX (1+/A), AZA (2+/C), MMF (2++/B), ciclosporin (2+/C) and other calcineurin inhibitors (3/D) should be considered in cases of arthritis, cutaneous disease, serositis, vasculitis or cytopaenias if HCQ is insufficient (SOA 97%).

(iii) For refractory cases, belimumab (1+/B) or rituximab (2+/C) may be considered (SOA 98%).

Rationale

Overview of the management of moderate lupus

Immunosuppressive cytotoxic agents should be used with CSs, while continuing anti-malarials and avoidance of UV radiation, to reduce disease activity in moderate lupus (Table 7), prevent the risk of further flares and lower the risk of damage accrual due to disease and CSs, because they act as steroid-sparing agents. Despite their widespread use in clinical practice and as background standard of care therapy in clinical trials, there are only a few RCTs demonstrating the efficacy of CSs and other immunosuppressive agents for the management of moderate lupus. Additional drugs should be considered if HCQ is insufficient or not tolerated and can be used in addition to HCQ. The evidence supporting the use of MTX has been discussed above, and the evidence supporting the use of CSs, AZA, MMF, calcineurin inhibitors (ciclosporin and tacrolimus) and LEF are discussed in this section. For patients who do not respond to these drugs, the biologic drugs rituximab and belimumab may be considered. It should be noted that there is a specific NHS England 2013 Interim Clinical Commissioning Policy Statement for rituximab in adult SLE patients [267], and NICE guidance for the use of belimumab in active autoantibody-positive SLE in adults has been published in 2016 [324]. Patients being considered for these drugs should be discussed with and/or seen by a specialist lupus centre with experience in using these drugs. The patients should meet specific criteria and be entered in to the BILAG Biologics Register (see below and Fig. 1). For patients not requiring biologics, suggested initial target dosing regimens for active disease (as used in most studies) and lower maintenance dosing regimens to prevent recurrence of disease once patients are stable are shown in Table 7. The actual regimen used for individual patients will depend on the clinical picture and the treatment history. It is important to increase the dose and/or change treatment if patients fail to respond in the expected time frame. The LOEs and GORs for all the drugs used to treat lupus are summarized in Table 2.

CSs for moderate lupus

Summary

Higher doses of oral CSs are required initially than are required for mild lupus, for example prednisolone at up

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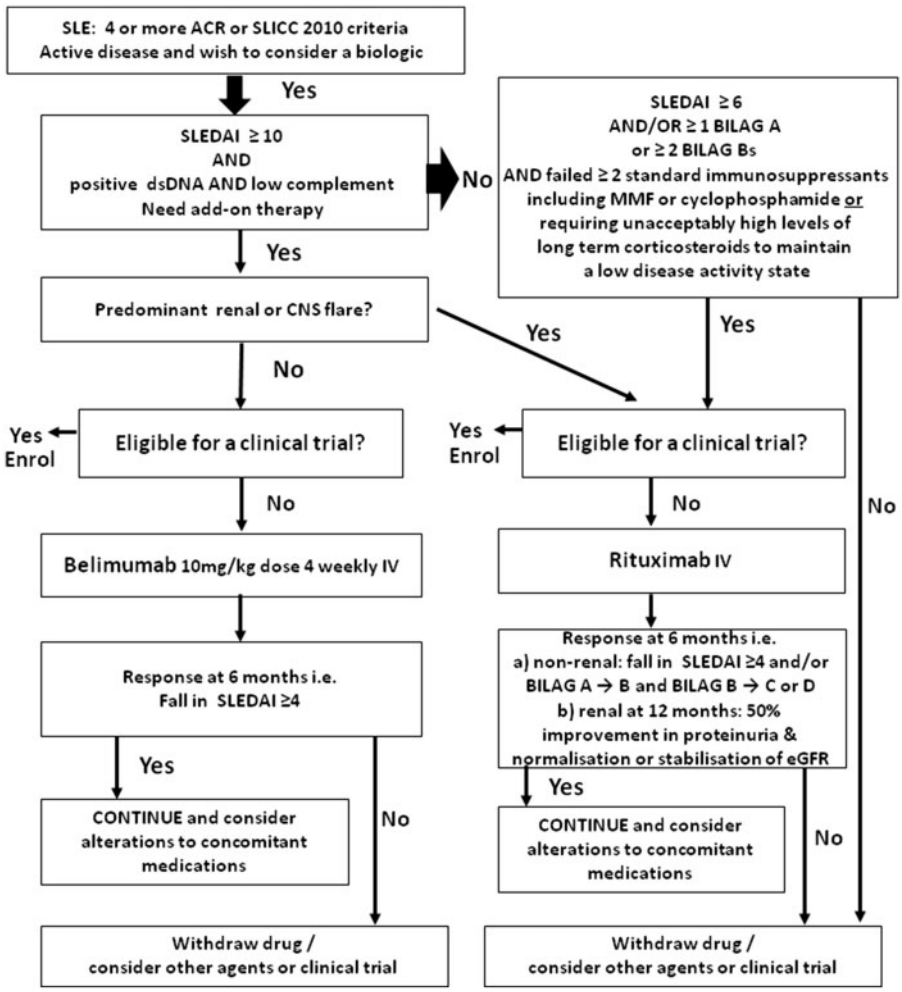
FIG. 1 Summary of NICE and NHS England guidance for the use of belimumab and rituximab in patients with SLE



Belimumab is licensed and NICE-approved (Belimumab for active autoantibody-positive systemic lupus erythematosus: TA397, published June 2016) and should be considered first [324]. Rituximab is not licensed and should only be used according to the NHS England Interim Clinical Commissioning Policy Statement: rituximab for the treatment of systemic lupus erythematosus in adults: published September 2013 A13/PS/a [267]. All patients receiving either drug must be enrolled in the BILAG Biologics Register and be managed at or in collaboration with a specialized centre.

to 0.5 mg/kg/day, and intermittent treatment with i.m. 80–120 mg MP or even i.v. doses of MP (up to 250 mg) are used as well as, or instead of, oral prednisolone to promote a quicker response with less total CS exposure. Prednisolone dosing should be reduced, as disease activity improves, to the lowest possible maintenance dose and stopped, if possible, as other immunosuppressive agents take effect over several weeks or months.

Evidence

There are no data comparing different oral CS regimens for the treatment of moderate lupus. Two controlled studies have shown that treating patients who are clinically stable but showing serological deterioration with a short course of moderate-dose CSs (e.g. 30 mg/day) can prevent more flares than placebo and lead to improvement in serological markers [46, 60]. However, there is a risk of treating patients that will not flare, and this approach is not recommended due to the side effects of CSs.

There are some data supporting the use of 100 mg i.v. MP pulses in non-renal lupus as an alternative to 1000 mg pulses [143], and for 1000 mg pulses on three occasions in patients with moderate or severe lupus, with very little oral prednisolone [146]. The data supporting the use of i.v. pulses of 500 or 1000 mg are discussed further below in the section on the management of severe lupus [148, 326]. There is one open-label RCT [142] comparing triamcinolone 100 mg given as an i.m. injection with a short course of oral MP tapered over 1 week. Overall, there was little difference between the regimens but some improvement was seen more quickly with the triamcinolone injection.

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Conclusions

Overall the LOE for CSs by i.m. or i.v. injection in non-renal moderate lupus is 2+ and GOR is C.

AZA for moderate lupus (non-renal disease)

Summary

AZA is not licensed for the treatment of lupus, but has been used for over 40 years, and it is the most frequently used cytotoxic agent [327] in lupus. AZA treatment (1–2.5 mg/kg/day orally) has been associated with prevention of flares and a reduction in CS dosage (see below and Table 2). It is usually started in patients with moderate lupus activity (Table 7) in conjunction with CSs, as it can take up to 3 months to be effective. It is also used for maintenance therapy after remission or significant response has been achieved with other agents used to treat severe lupus (such as CYC) that are less suitable for long-term therapy, particularly in women desiring pregnancy, or who are pregnant or breast-feeding [24, 25, 239, 328]. Most of the evidence (and the only double-blind RCTs) supporting its use relate to the management of LN [24, 25]. Only papers discussing the management of non-renal lupus with AZA are discussed here, although in some cases the studies included renal and non-renal patients. There is no evidence that it prevents atherosclerosis or other forms of damage [12, 329].

Evidence

The first reports of AZA being used for renal and non-renal manifestations of lupus with CSs appeared in the late 1960s and 1970s [149–151, 153, 330, 331]. Reduction in disease activity and flare rate and steroid-sparing effects were demonstrated in most of these open-label, controlled studies and in a case series [158]. AZA 200 mg daily was associated with an increased risk of significant liver dysfunction. There was no increased risk of infection, even starting at 3–4 mg/kg/day, but subsequent studies have used 2–2.5 mg/kg/day.

A prospective longitudinal open-label study [154] involving 17 SLE patients showed that AZA reduced lupus activity and anti-dsDNA antibody levels. Subsequently, in a retrospective study [155] with 61 SLE patients, suppression of anti-dsDNA antibodies by AZA (2 mg/kg/day) and low-dose prednisolone (7–12 mg/day) was associated with efficacy and better long-term outcome. However, the presence of renal disease, persistence of anti-dsDNA antibodies for at least 1 year after the beginning of treatment and reduction in AZA dosage to below 2 mg/kg/day predicted flares and was associated with a higher rate of lupus-related death.

An open-label, multicentre, RCT study of 89 SLE patients requiring 15 mg or more of prednisolone compared AZA (mean dose 2.1 mg/kg/day) with ciclosporin (mean dose 2.2 mg/kg/day) for its steroid-sparing properties [152]. The absolute mean change in prednisolone dose at 12 months, adjusted for baseline prednisolone dose, was not significantly different: 9.0 mg for ciclosporin (95% CI: 7.2, 10.8) and 10.7 mg for AZA (95% CI: 8.8, 12.7). There was no difference between groups in change in disease activity or number of flares, development of new damage, change in quality of life or numbers of patients discontinuing study drugs due to adverse events or lack of efficacy [152]. The conclusion was that both drugs can be used in lupus for their steroid-sparing properties, with appropriate monitoring.

AZA is usually well tolerated [332]. The main adverse events are nausea and vomiting, diarrhoea, flu-like illness with fever, rash, leucopenia and hepatotoxicity [156, 157, 332–334]. Side effects can occur soon after starting AZA and may require drug withdrawal [156, 335]. Hepatic veno-occlusive disease is a rare adverse event, but autoimmune hepatitis can improve on AZA, so this is not a contra-indication to its use [157]. AZA is not excreted by the kidney, and it can be used in patients with renal impairment. Managing patients with lupus-related leucopenia with AZA can be difficult [332, 336]. The enzyme thiopurine S-methyltransferase (TPMT) catalyses the inactivation of AZA. It is worth testing patients for TPMT [334] before starting AZA, as the very low level phenotype (homozygous deficiency that occurs in 0.3% Caucasians) is associated with potentially life-threatening bone marrow toxicity; otherwise, weekly full blood counts are required as the dose is increased over several weeks [337, 338]. Those patients with intermediate TPMT levels due to a heterozygous state have an increased risk of leucopenia as well, and such testing does not remove the need for monitoring the effects of the drug on the full blood count [156, 332] and liver function according to national or local guidelines [337, 338].

AZA does not cause infertility and has not been found to be teratogenic in clinical practice, despite theoretical concerns [339, 340]; thus, it can be used in women planning conception and is compatible with pregnancy and breast-feeding [24, 98, 239]. It may reduce the response to some immunizations [341–344], but this is not a contra-indication to immunization except with live viruses [74, 292]. There is no evidence that AZA increases the risk of malignancy in lupus patients [301, 345], but it may increase the risk of cervical dysplasia [346].

Conclusions

Although the data for AZA in non-renal lupus are much weaker than the data supporting its use in LN (see below), there are four open-label RCTs, three prospective cohort studies, two retrospective cohort studies and one case series supporting the use of AZA for non-renal lupus: overall LOE 2+, GOR C.

MMF for moderate lupus (non-renal disease)

Summary

There are increasing data showing that MMF in combination with CSs reduces moderate and severe lupus disease activity, reduces renal and non-renal flares, is associated with CS-sparing properties and is tolerated well (see Tables 2 and 7 for suggested treatment strategies). However, there are no placebo-controlled double-blind RCTs specifically designed to assess the use of MMF in non-renal lupus. It is teratogenic and is contra-

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indicated in women trying to conceive, or who are pregnant or breast-feeding.

Evidence

The first systematic review of MMF (2–3 g daily) in non-renal lupus was published by Mok in 2007 [170] and reviewed 20 papers in terms of the response of specific clinical features (up to 2006) and steroid-sparing properties. This systematic review included patients mostly refractory to other therapies who were treated with MMF in uncontrolled studies for arthritis, renal, haematological and cutaneous manifestations, and a few with neuropsychiatric manifestations, and also covered the use of MMF in prevention of flare in a small prospective study of patients with rising anti-dsDNA antibody levels [162–164, 347].

A later systematic review [133] with a literature search up to end of October 2011 provided further evidence that MMF treatment is associated with reductions in disease activity, flare rate and prednisone dose and included data from five cohort studies [162–166] and from the Aspreva Lupus Management Study (ALMS) trial in LN that specifically reported on non-renal lupus manifestations (see below) [159]. Further supporting evidence for MMF comes from a small case series [169] and a study [348] showing that mycophenolic acid (MPA) levels vary between patients and that higher trough levels were associated with less risk of disease flare. MPA levels were more closely associated with efficacy and safety than the dose of MMF. This test is available in some hospitals, but the target trough level of 3.5–4.5 mg/l was recommended to be tested in a controlled trial before being widely applied.

The beneficial effects of MMF on non-renal disease activity [159] were demonstrated in a 6-month open-label RCT (ALMS) that compared oral MMF (target dose 3 g/day, median exposure 2.6 g/day) with pulses of i.v. CYC (0.5–1.0 g/month) as induction treatment for biopsy-proven LN [349]. All patients received prednisone starting at 60 mg/day that was tapered to 10 mg/day. There was induction of remission in $>$80% of patients treated with MMF for active disease at baseline in mucocutaneous, musculoskeletal, cardiorespiratory and vasculitis systems in addition to renal response in 56% (the primary end point) [349]. There were no flares in the patients on MMF, and complement levels and titres of anti-dsDNA antibodies normalized. Very similar renal and non-renal responses were seen in those given CYC [159]. However, more Black and Hispanic patients responded to MMF than i.v. CYC, and further trials are required to assess the role of race, ethnicity and geographical region on treatment response [350].

In the maintenance phase of ALMS [160], 227 patients from the 6-month induction study who met the renal clinical response criteria were randomized again to MMF (2 g/day) or AZA (2 mg/kg/day) in a 36-month, double-blind, double-dummy, phase III RCT [160]. Prednisolone $\leqslant$10 mg/day or its equivalent was allowed and was taken by 90% of the MMF group ($n = 116$) and 87% of the AZA group ($n = 111$). Secondary end points included an analysis of non-renal severe flare. Severe non-renal flare rates did not differ between groups: 6.9% for the MMF group and 6.3% for the AZA group. There were no significant differences in the changes in anti-dsDNA antibodies or complement levels between groups. However, MMF was superior to AZA in various renal parameters related to maintaining a renal response and in preventing renal relapse in these LN patients, irrespective of which induction treatment had led to their initial response, race and geographical region [160]. Adverse events were common in both groups ($>$95%) (mostly minor infections and gastrointestinal disorders). Serious adverse events occurred in 24% of the MMF group and 33% of the AZA group ($P = 0.11$). The rate of withdrawal due to adverse events was lower with MMF than AZA (25% *vs* 40%, $P = 0.02$).

Another randomized open-label controlled trial [161], in Caucasians predominantly, compared MMF (mean 2 g/day) and AZA (mean 124 mg/day) for maintenance therapy over 36 months, starting at week 12 after induction with a short course of i.v. CYC (6 $\times$ 500 mg over 10 weeks) for the management of biopsy-proven proliferative LN. All patients initially received three i.v. pulses of MP and were tapered from 0.5 mg/kg/day prednisone down to 5 mg/day at week 52 and then tapered further and stopped if possible. Both regimens were well tolerated, and there was comparable improvement in renal end points and non-renal parameters, including disease activity indices and C3 levels in both groups. There were less renal flares and less haematological adverse events with MMF than AZA (though this was not statistically significant in this study).

Since the systematic review [133], further studies reporting reduction in disease activity included a retrospective review of patients treated with MMF that found a significant reduction in mean weekly steroid dosage (from about 12.5 to 3 mg/day prednisone) [167]. A single-centre retrospective cohort study [168] involving 135 patients with SLE (50% with renal disease) and 43 patients with systemic vasculitis treated with MMF reported good responses in 46% of patients, and the mean prednisolone dosage was significantly reduced from 22 to 8 mg/day at 12 months. These and other studies have shown that adverse events occur in up to 44% of patients over 5 years: mostly mild gastrointestinal intolerance and infections, with leucopenia and hospitalization rare. In one study most patients tolerated the drug well, with 73% of patients on the drug at 12 months, and there was no relationship between adverse events and dose (250 mg to 3 g daily) [351]. However, there have been increasing reports of teratogenicity, and it should be stopped at least 6 weeks before a planned pregnancy, and MMF should not be taken by women who are pregnant or breast-feeding [239].

Yahya *et al.* [172] reported on a small open-label prospective study of 14 non-renal lupus patients randomized to mycophenolate sodium (MS) or standard care and showed that MS treatment was safe and was associated with reduced disease activity. A randomized open-label

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trial [171] of 40 patients with primary systemic vasculitis or SLE compared MMF (2000 mg/day) and enteric-coated MS (1440 mg/day). The composite primary end point was treatment failure and/or drug intolerance over 12 months. MS was anticipated to be tolerated better, but no difference in tolerance was observed. Although MS was associated with slightly better efficacy, this may have been due to imbalance in factors affecting remission and relapse, despite randomization with minimization. This study did not support the use of MS as a better tolerated and efficacious alternative to MMF for routine use, but MS could be considered in patients with gastrointestinal side effects from MMF.

Conclusions

The evidence that MMF reduces disease activity, lupus flare and has steroid-sparing properties in non-renal lupus comes from two systematic reviews, three open-label RCTs in LN and seven cohort studies: LOE 2++, GOR B. MPA/sodium (MS) may be considered in patients intolerant of MMF based on two studies (LOE three, GOR D).

Ciclosporin and tacrolimus for moderate lupus (non-renal disease)

Summary

Ciclosporin and tacrolimus do not cause myelosuppression and have the ability to reduce moderate disease activity (Tables 2 and 7). There is more evidence for ciclosporin in non-renal lupus, and it has been particularly helpful in the treatment of cytopenias, where there is likely to be difficulty distinguishing cytopenias due to lupus from cytopenias due to drugs such as AZA, MTX and MMF. Both ciclosporin and tacrolimus can be used (at the lowest possible dose) in women planning pregnancy, and in those who are pregnant or breast-feeding [239].

Evidence

There are two open-label RCTs [152, 173] and eight non-renal cohort studies supporting the use of ciclosporin at doses of $\leqslant$2.5 mg/kg/day in patients with normal renal function, although a systematic review [133] that included details of two open-label RCTs and a brief summary of six of the cohort studies reported that there was not much evidence supporting the use of ciclosporin in lupus because there were no double-blind, placebo-controlled RCTs.

Nevertheless, the open-label RCTs suggested that ciclosporin reduced disease activity as well as AZA did [152] and better than CSs alone [173], and that ciclosporin treatment was associated with significant CS-sparing properties in both RCTs, equivalent to that of AZA in one trial [152] as reported previously by the cohort studies. These included two prospective cohort studies [174, 175] that showed significant reduction in disease activity at 6 months, with most benefit in patients with renal and/or haematological manifestations, and response maintained to 24 months in one study [175]. Three retrospective studies [176–178] reported a reduction in disease activity and/or flares (particularly haematological manifestations such as thrombocytopenia), and significant steroid-sparing properties were reported in two of these studies [175, 177].

In the first of two additional studies not mentioned in the systematic review, ciclosporin was shown to treat thrombocytopenia in six patients [179], three of whom were able to stop CSs. In the second study [180], a retrospective cohort study, ciclosporin was used to manage 40 refractory lupus patients, including 11 patients with neurological conditions and 7 with overlap syndromes, as well as 18 with LN. The study showed reduction in disease activity and only mild transient adverse events not requiring discontinuation.

Adverse events were the focus of another study [181] with doses up to 5 mg/kg/day, so it was not surprising that adverse events were reported in 63%, but these led to discontinuation in only 16% and were reversible within 3 months of stopping the drug, consistent with many other reports. Ciclosporin treatment can cause hypertrichosis, gum hypertrophy, hypertension, paresthesiae, tremor, gastrointestinal symptoms and impaired renal function, especially at higher doses ($>$3 mg/kg/day). It is best used at lower doses ($\leqslant$2.5 mg/kg/day) as that is more tolerable and rarely causes permanent nephrotoxicity if carefully monitored. In the open-label RCT [152], there were no unexpected adverse events, and with appropriate monitoring of renal function and blood pressure, it was not discontinued due to adverse events or inefficacy more often than AZA.

There are two reports of tacrolimus in non-renal lupus and they were included in the systematic review [133]. The first was a small retrospective cohort study [182] with 10 non-renal patients showing significant reductions in SLEDAI and prednisolone over 1 year on 1–3 mg daily. The second was an open-label prospective study [183] with 21 mostly non-renal patients showing reduction in SLEDAI score over 6 months and no serious side effects, but 29% withdrew due to inefficacy and 10% due to adverse events.

Conclusions

Overall, the LOE for ciclosporin in non-renal lupus from two open-label RCTs, eight non-renal cohort studies and one systematic review is 2+ and GOR is C.

The LOE for tacrolimus from two studies in non-renal lupus and one systematic review is three and GOR is D.

LEF in moderate lupus

Summary

The systematic review [133] and our search found little evidence for efficacy and safety of LEF in lupus patients, with only two small studies in the literature. This drug can be considered in patients refractory to, not suitable for or intolerant of MTX, AZA, MMF and calcineurin inhibitors, for whom CYC, rituximab and belimumab are not suitable or not available. It is not suitable for women considering pregnancy, and a cholestyramine washout is required if pregnancy is desired or occurs while it is being taken [239].

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Evidence

There was a randomized, double-blind, placebo-controlled trial in moderate SLE patients, with only six patients in each group [184]. A significant reduction in SLEDAI and prednisone occurred in both groups over 24 weeks. The LEF group showed significantly greater mean reduction in SLEDAI score, but there was no difference in steroid reduction between the groups. Side effects included transiently abnormal alanine aminotransferase (ALT), leucopenia and hypertension. There was a retrospective analysis of 18 patients who received LEF [185], but 4 patients withdrew (3 due to adverse events, including 1 with rash), and only 9/14 achieved lower SLEDAI scores after 2–3 months of therapy.

Conclusions

Overall the LOE for LEF for reducing non-renal lupus disease activity from two studies is three and the GOR is D. Caution is advised about its use in those with pre-existing subacute cutaneous lupus, as this may worsen as observed in other non-lupus studies.

Rituximab for refractory moderate lupus

Summary

Rituximab can be prescribed and reimbursed in the UK currently according to the NHS England 2013 Interim Clinical Commissioning Policy Statement for rituximab in adult SLE patients [267] who have two or more systems with BILAG B scores; or have severe BILAG A level disease activity, using the BILAG-2004 index [268, 269]; or have a SLEDAI-2 K score [270] >6 if they have failed two or more immunosuppressive agents (due to inefficacy or intolerance), at least one of which must be MMF or CYC; or need unacceptably high doses of steroids to achieve lower level of disease activity.

The patients must be managed in conjunction with a specialist centre for lupus and be entered in to the BILAG Biologics Register for standardized reporting of outcome (see Fig. 1 flowchart for eligibility and response criteria). This is essential for providing more open-label data in a prospective study with control patients treated with other immunosuppressive therapies, given the failure of the international double-blind, placebo-controlled lupus trials to meet their primary end points, as discussed below (EXPLORER for active non-renal disease [190, 191] and LUNAR for LN [352]). This policy was agreed as a result of the increasing published evidence supporting the efficacy of rituximab in refractory lupus patients, who are likely to differ from those recruited to trials where there was no requirement to have failed conventional therapy. Pregnancy should be avoided for at least 6 months after exposure to rituximab [239].

Evidence

The current evidence supporting the efficacy and safety of rituximab in non-renal lupus was most recently reported in a systematic review [200] in 2014 by Cobo-Ibanez with a literature search up to June 2013. This included the non-renal RCT EXPLORER [190] and its exploratory analysis [191], 2 open-label phase I/II trials [192, 193] and 22 cohort studies which analysed 1231 patients in total [200]. The 2 open-label trials [192, 193] and 5 of the cohort studies had been discussed in a previous systematic review summarizing off-label use in 188 cases (including non-renal and renal patients in 9 cohort studies and 26 case series/reports published up to December 2007) [202].

The non-renal patients discussed in the systematic review by Cobo-Ibáñez *et al.* [200] were heterogeneous, but in general had active lupus disease unresponsive to steroids and/or immunosuppressants prior to treatment with rituximab. Treatment with rituximab was associated with a reduction in global disease activity over 3–9 months, with 64–91% achieving response, including patients with a reduction in complement and anti-dsDNA antibody levels, arthritis and thrombocytopenia. Evidence for a steroid-sparing effect was based on the 2 open-label trials and 10 of the cohort studies [200]. There were few significant adverse events in the RCT, 2 open-label studies and 20 cohort studies [200]. Relapses/flares did occur at variable times (3.7–18 months), although in the RCT there were numerically fewer severe BILAG A flares and longer time to these flares in the rituximab group compared with the placebo group, and this almost achieved statistical significance (hazard ratio = 0.61, P = 0.052) [191]. Better clinical response after a second course was observed in 2 of the cohorts that studied retreatment [200], and a further report supported this observation and that steroid reduction occurred after each of two courses of rituximab [199]. The evidence for rituximab treating mucocutaneous involvement was deemed weak [200], and this may be explained by a recent report [353] specifically addressing 26 SLE patients with various subtypes of lupus rash, which observed that acute lupus rash responded whereas chronic cutaneous lupus (such as discoid rash) did not respond to rituximab and that new lesions with typical histology may appear despite confirmed B cell depletion.

Rituximab treatment early in the course of lupus disease, followed by AZA, was tried by Ezeonyeji *et al.* [194] specifically for its steroid-sparing effect in a pilot study with 8 SLE patients whose results were compared with 23 matched historical control patients treated conventionally [194]. Reduction in disease activity, a fall in anti-dsDNA antibodies and complement, and significant lower cumulative prednisolone at 6 months compared with controls was observed. There is also an open-label LN study suggesting that early rituximab with i.v. MP followed by MMF may avoid the use of oral CSs, and this regimen is currently being tested in a controlled randomized RCT called RITUXILUP [354].

The Duxbury systematic review and meta-analysis [201] reported response rates for various disease activity measures for patients in the open-label studies of refractory lupus treated with rituximab also reviewed by Cobo-Ibáñez *et al.* [200]. The Duxbury review and meta-analysis

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did include a section on LN (not discussed here) and included a few non-renal studies not in the Cobo-Ibáñez review, although the latter also included a few not in the Duxbury review. The BILAG index was used in 188 patients treated with rituximab in 8 open-label studies (3 prospective, 4 retrospective and 1 small case–control) [201]. The pooled global response in seven of these studies was 83%. The complete response rate was 47% and the partial response rate was 38% in six studies. A significant reduction in anti-dsDNA antibodies was observed in 6 of the 8 studies and a significant rise in complement was observed in 5 of 6 studies. Various versions of the SLEDAI were used in 513 patients treated with rituximab in 12 open-label studies: 5 prospective, 6 retrospective and 1 open-label randomized trial, only 1 of which also analysed BILAG response. With SLEDAI the global response was 77% in 11 studies. In 6 studies the complete response rate was 57% and the partial response rate was 31%. Anti-dsDNA levels fell in 3 of 3 studies and complement rose in 2 of 3 studies [201].

Publications from cohorts in Germany [195], Italy [196] and Japan [197] have confirmed similar levels of efficacy with various disease activity measures and provided further safety data in another 264 patients. Long-term follow-up of 98 SLE patients treated with rituximab over a 12-year period has shown in a retrospective analysis that the group with longer duration of depletion ($\geqslant$12 months) was associated with a better response (greater decrease in BILAG score at 6 and 12 months) than those with shorter period of B cell depletion [198].

The results of these open-label studies are much better than the response rates observed in the EXPLORER RCT (for rituximab *vs* placebo: complete 12% *vs* 16%, partial 17% *vs* 13%) [190]. However, EXPLORER used more stringent BILAG response criteria than used in any other study [201], but did observe a reduced rate and time to severe BILAG A flare [191]. High-dose CSs and background immunosuppression were used in both arms of the EXPLORER trial and may have reduced the ability to discriminate benefit from rituximab [201]. Patients on MTX as the background immunosuppressant derived more benefit from rituximab in a *post hoc* analysis than those in the placebo group [190], and in contrast to those on background AZA or MMF [190]. Patients of Afro-American or Hispanic origin were also shown to benefit from rituximab in the RCT, in contrast to Caucasians [190].

However, two case series reports have suggested that repeat courses of rituximab may increase the risk of hypogammaglobulinaemia and infection [199, 293]. Progressive multifocal leukoencephalopathy (PML) has been reported in 17 SLE patients, of whom 5 had been treated with rituximab. It seems likely that immunosuppression, however it is achieved, is the key factor in the development of PML. Lupus patients may be at increased risk of developing PML compared with other rheumatic diseases [355]. The risk of rituximab causing PML in rheumatic diseases, including RA and SLE, has been estimated at 5/100 000, which is less than the risk observed with some other immunosuppressants in other diseases [356].

Conclusions

There is now considerable evidence for the ability of rituximab to reduce disease activity in refractory non-renal SLE of moderate and severe severity, albeit mostly from cohort studies. There have been relatively few concerns in the individual reports and systematic reviews about adverse events, including infections, in lupus patients on rituximab. There is increasing evidence that rituximab has steroid-sparing properties, but further evidence for its use early in the disease course is needed. Overall, the LOE for rituximab from 3 systematic reviews (including a meta-analysis and 30 studies, including 1 RCT and 3 open-label trials for reducing disease activity and for steroid-sparing properties) is 2+ and the GOR is C.

Belimumab for refractory moderate lupus

Summary

There have been two large phase III RCTs [203, 204] investigating the use of belimumab in moderate–severe seropositive lupus (mostly musculoskeletal and cutaneous disease; as severe active renal and NPSLE disease were exclusions). All patients received steroids, HCQ and/or immunosuppressive drugs, with specific criteria for dosing changes allowed or contra-indicated in the protocol. Both trials showed a significantly increased proportion of responders to belimumab at a 10 mg/kg dose in addition to standard care. A variety of secondary end points were met, and there were no significant differences in adverse events, leading to the drug being approved and licensed by the US Food and Drug Administration and the European Medicines Agency. NICE guidance for use of belimumab in active autoantibody-positive SLE in adults has been published [324] and is summarized in Fig. 1. Patients must have positive anti-dsDNA antibodies, low complement and a SELENA-SLEDAI score $\geqslant$10 despite standard therapy. Patients should be recruited to the BILAG Biologics Register so that outcomes can be recorded, and treatment with belimumab should not be continued for $>$24 weeks unless the SELENA-SLEDAI score has improved by 4 points or more. Pregnancy should not occur while on belimumab, but first trimester exposure is unlikely to be harmful [239].

Evidence

In the BLISS52 trial [203], at week 52 the response rate with placebo was 44%, with belimumab 1 mg/kg it was 51% ($P = 0.013$) and with 10 mg/kg it was 58% ($P = 0.001$). In the BLISS76 trial [204], the placebo response rate at week 52 was 34%, with belimumab 1 mg/kg it was 41% ($P = 0.089$) and with 10 mg/kg it was 43% ($P = 0.017$). The response rates at week 76 were a little lower in all groups. A meta-analysis of the response at 52 weeks in the phase II trial of belimumab [205] as well as BLISS 52 and BLISS 76 trials showed benefit for belimumab, with an odds ratio of 1.63 (95% CI: 1.27, 2.09) [209]. Safety data from the phase II trial and its open-label extension have not shown any significant concerns and continued benefit for up to 7 years [207, 208]. The most common side effects have been upper respiratory tract and urinary tract infections,

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arthralgia, headaches, fatigue and nausea. Serious infusion reactions and infections have been rare [207, 208]. There have been two case reports of progressive multifocal leukoencephalopathy [357, 358], but there is no evidence that belimumab increases the risk more than other immunosuppressive regimens in SLE patients [356].

Further *post hoc* analyses [359, 360] on the pooled datasets from BLISS 52 and BLISS 76 trials have demonstrated that belimumab therapy was associated with significantly more patients showing improvements than with placebo in the most commonly affected musculoskeletal and mucocutaneous systems, and more immunological abnormalities normalized than with placebo [359]. Improvement was reported less consistently in other systems that were less often affected [359]. There was less worsening in haematological, immunological and renal parameters in those patients on belimumab than in those on placebo [359], but as with improvement, effects were not always dose related. Serological improvements (reduction in anti-dsDNA antibodies and increase in C3/C4 levels, without reduction in memory T or B cell numbers or levels of anti-pneumococcal or anti-tetanus toxoid antibodies) have been reported [361]. This is consistent with the low rate of serious infections in the long-term open-label study of belimumab [207, 208].

Another pooled analysis of BLISS 52 and BLISS 76 trials identified that belimumab had most therapeutic benefit compared with standard therapy alone in patients with higher disease activity (SELENA-SLEDAI $\geqslant$10), positive anti-dsDNA antibodies, low complement, or CS treatment at baseline [206]. Week 52 response rates in the low complement/anti-dsDNA–positive subgroup were 32% for placebo, 42% for belimumab 1 mg/kg ($P = 0.002$) and 52% for belimumab 10 mg/kg groups ($P < 0.001$). For the SELENA-SLEDAI $\geqslant$10 subgroup, the response rates were 44%, 58% ($P < 0.001$) and 63% ($P < 0.001$), respectively. Belimumab was also shown to reduce severe flares and CS use and to improve health-related quality of life most in these more severe subgroups [206]. These analyses contributed to the decision by the European Medicines Agency to limit the market authorization for belimumab (Benlysta) to add-on therapy in adult patients with active autoantibody-positive SLE with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy [362].

Conclusions

Treatment with belimumab in addition to standard therapy in autoantibody-positive SLE patients was associated with some improvements in clinical, laboratory and patient-reported outcome measures (compared with placebo in addition to standard therapy) and had a low risk of serious side effects. Based on the results of the two RCTs and the *post hoc* analyses, belimumab is considered by NICE to be cost-effective in the UK only for patients who meet the specific criteria [324] (see summary above and Fig. 1), so availability is limited. The drug is being used in other countries, particularly in the USA, where the licence covers patients with moderate disease activity and only specifies that patients must have active, autoantibody-positive lupus and be receiving standard therapy (such as CSs, antimalarials, immunosuppressives and NSAIDs) [363]. Overall, the LOE for belimumab in non-renal lupus from a meta-analysis, one phase II study, two phase III RCTs, their open-label extension study and *post hoc* analyses combining the data from the two RCTs is 1+ and the GOR is B.

Recommendations for the management of severe SLE

(i) Patients who present with severe SLE, including renal and NP manifestations, need thorough investigation to exclude other aetiologies, including infection (4/D). Treatment is dependent on the underlying aetiology (inflammatory and/or thrombotic), and patients should be treated accordingly with immunosuppression and/or anticoagulation, respectively (4/D) (SOA 98%).

(ii) Immunosuppressive regimens for severe active SLE involve i.v. MP (2+/C) or high-dose oral prednisolone (up to 1 mg/kg/day) (4/D) to induce remission, either on their own or more often as part of a treatment protocol with another immunosuppressive drug (4/D) (SOA 98%).

(iii) MMF or CYC are used for most cases of LN and for refractory, severe non-renal disease (2 ++/B) (SOA 98%).

(iv) Biologic therapies belimumab (1+/B) or rituximab (2+/C) may be considered, on a case-by-case basis, where patients have failed to respond to other immunosuppressive drugs, due to inefficacy or intolerance (SOA 98%).

(v) IVIG (2−/D) and plasmapheresis (3/D) may be considered in patients with refractory cytopaenias, thrombotic thrombocytopaenic purpura (TTP) (1+/B), rapidly deteriorating acute confusional state and the catastrophic variant of APS (SOA 93%).

Rationale

Overview of the management of severe lupus

Patients who have serious manifestations with organ- or life-threatening disease require treatment with intensive immunosuppression followed by a prolonged period of less aggressive maintenance therapy to prevent relapse (summarized with suggested dosing regimens in Table 7). In some cases there may be a thrombotic component to the clinical features that requires anticoagulation, for example in patients with APS as well as lupus. There is most evidence for the management of LN, less for neuropsychiatric disease and very little for other organ-specific manifestations.

The authors of this guideline have not reviewed the evidence for the management of LN as they suggest that the EULAR/ERA-EDTA recommendations for the management of adult and paediatric LN [24] are followed. The main recommendations and SOAs with them are shown in Table 3. Further details about these recommendations and the evidence for them have been published [24].

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For the management of severe non-renal SLE, the evidence for treatment with high-dose CSs, AZA, CYC, MMF, rituximab, IVIG and plasma exchange (plasmapheresis) is discussed below. The evidence for use of belimumab and of the calcineurin inhibitors ciclosporin and tacrolimus, particularly for cytopenias due to lupus, has already been reviewed above. Suggested initial target dosing regimens and lower maintenance regimens to prevent flares once patients are stable are shown in Table 7. The actual regimen used for individual patients will depend on the clinical picture and the treatment history. Patients with refractory disease, especially those being considered for belimumab and rituximab, should be discussed with and/or seen by a specialist lupus centre (see Fig. 1 flowchart for eligibility and response criteria). It is important to review the response regularly and to increase the dose and/or change the treatment if patients fail to respond.

CSs for severe SLE

Summary

The emphasis in the last 10 years has been on finding steroid-sparing regimens to treat severe lupus, using other immunosuppressants in conjunction with CSs (either orally, intravenously or both), to induce and maintain response with the least risk of adverse events, particularly infection. In general, there is an increasing tendency to use oral prednisolone at a dose of 0.5 mg/kg/day with i.v. MP pulses (3 $\times$ 500–750 mg) rather than higher doses of i.v. MP pulses and/or higher dose of oral prednisolone (e.g. 0.75–1 mg/kg/day) as done in the past for all severe manifestations of lupus.

Evidence

I.v. MP pulses as an alternative to, or in addition to, high-dose oral prednisolone was first reported as a treatment for LN [24, 325, 326]. I.v. MP pulses were introduced for the management of non-renal lupus in the early 1980s [147]. An open-label cohort study [146] and an open-label trial [145] using i.v. MP pulses followed by alternate day oral CSs found that pulse therapy led to rapid improvement in clinical symptoms and anti-dsDNA and C3 levels, but that an alternate day oral regimen was associated with relapses. A small double-blind, placebo-controlled RCT with mostly non-renal SLE patients [144] found that 3 i.v. MP pulses resulted in faster and more complete improvement in the first 2 weeks in 12 patients with SLE, but there was no significant difference in efficacy or safety parameters at 4 weeks or 6 months compared with the placebo group; however, all patients received 40–60 mg of oral prednisolone daily [144].

A double-blind RCT [143] comparing three daily i.v. MP pulses of either 1000 or 100 mg in 21 patients with SLE causing fever, cardiorespiratory, renal or NP manifestations (with individualized outcomes based on entry manifestations) suggested no difference in efficacy between the regimens. A retrospective study compared low-dose i.v. MP pulses ($\leqslant$1500 mg over 3 days) with high-dose pulses (3–5 g over 3–5 days) for the treatment of severe flares [148]. This study suggested that the lower dose was sufficient and safer for controlling SLE flares than the high-dose regimen, which was associated with an increased number of infections [148].

Conclusions

There is limited evidence for any particular CS regimen for specific manifestations of severe non-renal lupus. Overall the LOE for i.v. MP pulses and oral prednisolone in non-renal severe lupus is 2+ and the GOR is C.

AZA in severe SLE

Summary

AZA (2–3 mg/kg/day) is sometimes used as first-line therapy with CSs in severe non-renal lupus (see Table 7), based on the evidence discussed in the section on the use of AZA for the management of moderate lupus. It is most often used in women planning pregnancy or pregnant, as it is much safer in pregnancy than CYC or MMF, which are contra-indicated in such situations [239].

Evidence

There was only one open-label controlled trial, with 24 patients with severe (life-threatening) multisystem manifestations of lupus [151], which showed no definite benefit from the addition of AZA compared with 40–60 mg prednisone alone for 6 months, before tapering over the next 18 months, although there was some steroid-sparing benefits seen at 12 months. It has been used as primary treatment at a dose of 2 mg/kg/day as an alternative to MMF or CYC in low-risk renal patients without adverse prognostic factors and when these drugs are contra-indicated, not tolerated or unavailable [24].

AZA has been used more often as maintenance therapy after a course of CYC for severe lupus, based on the evidence from studies undertaken in patients with LN [24, 25]. The rate of major extra-renal flares in the maintenance phase of the Aspreva Lupus Management Study (ALMS) study was low in the AZA group at 6.3% (7/111) and similar to the frequency of 6.9% (8/116) in the MMF group [160]. There is some evidence that AZA may be less effective at preventing renal flare in patients in this LN study than MMF, as discussed in the section on MMF [160]. However in a predominantly Caucasian LN population, in the MAINTAIN study, no difference in number or time of severe systemic flares in the AZA group (4/43) compared with the MMF group (3/53) was observed [161]. There are no trials or controlled studies addressing AZA as a primary treatment for neuropsychiatric lupus or any other specific serious non-renal manifestations of lupus, but it has been used after CYC for the treatment and prevention of recurrence of lupus psychosis in 13 patients [328].

The systematic review of non-biologic immunosuppressants in non-renal SLE by Pego-Reigosa *et al.* [133] only considered the unblinded RCT (showing no benefit) from 1975 [151] and a cohort study (showing a reduced rate of flare [155] in patients on AZA) and concluded that there was little evidence to support the use of AZA in non-renal lupus.

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Conclusions

Overall, the LOE for AZA in non-renal severe lupus is 2+ and the GOR is C.

CYC in severe SLE including LN and neuropsychiatric lupus

Summary

CYC, although not licensed for lupus, has been used for the treatment of severe lupus, particularly LN and organ- or life-threatening non-renal disease, since the late 1960s, with the first open-label trial in LN reported in 1971 [364]. Oral CYC is associated with an increased risk of bladder cancer and has been replaced by i.v. CYC pulses in the management of severe lupus. There is most experience with i.v. CYC pulses in LN and NPSLE (Tables 3 and 7). CYC is teratogenic and is contra-indicated in women trying to conceive, or who are pregnant or breast-feeding. It is gonadotoxic and can cause infertility, and men should not father children while on CYC [239].

Evidence

The first controlled trial comparing prednisone with CYC in LN, non-renal lupus and PM was reported in 1973 [365], and a similar design was used to compare oral CYC and AZA in lupus not responsive to 15 mg prednisolone [366], but numbers were small and the aim of matching individual patients and comparing their outcomes was unsuccessful. Since then, studies have used different trial designs and evidence supporting the use of various doses of oral and later i.v. pulse CYC regimens to reduce disease activity and prednisolone dosage and to improve outcomes in patients with LN and non-renal lupus have been reported. The best-known regimens are based on the National Institutes for Health i.v. CYC protocol (monthly i.v. CYC at 500–1000 mg/m^2 body surface area for 6 months, followed by 3 monthly i.v. CYC for 2 years) [367] and the Euro-Lupus protocol, which uses lower doses (500 mg fixed dose i.v. CYC 2-weekly for a total of 6 doses, followed by oral AZA) [368] and appears to be as effective and safer for LN in Europe than high-dose regimens [369]. In recent years, the 3-monthly i.v. CYC maintenance pulses for 2 years in the National Institutes for Health protocol have been replaced by oral MMF or AZA [25, 370].

I.v. CYC pulses were the most widely used regimes for all but the mildest cases of acute proliferative glomerulonephritis until MMF was found to be comparable in efficacy and safer [24, 25]. It should be noted that neither of these drugs is licensed for the treatment of LN, but both are supported as appropriate treatment for the management of LN in the EULAR/ERA-EDTA recommendations for the management of adult and paediatric LN [24] (Table 3) and the ACR guidelines for screening, treatment and management of LN [25].

Treatment regimens tested in LN have often been applied to severe non-renal lupus disease as there are fewer non-renal studies and they include heterogeneous patient populations. A systematic review [133] evaluated 29 studies, including 4 unblinded RCTs in which 3742 patients with non-renal lupus were treated with a variety of CYC regimens. There are more data on the efficacy and safety of using CYC to treat non-renal lupus than of any other drug treatment; however, there are fewer high-quality studies than for LN, and diverse end points have been used, making it hard to compare the studies.

Data from the ALMS RCT comparing i.v. CYC (0.5–1.0 g/m^2 monthly $\times$ 6) and MMF (target 3.0 g/day) as induction therapy for LN [159] showed that i.v. CYC therapy was associated with almost 95% response in all of the non-renal systems, apart from the haematology, which was confounded by drug-induced cytopenias and anaemia of uncertain cause. There was no difference in response between i.v. CYC or MMF in any of the systems studied, including renal.

Some of the best evidence supports the use of pulse i.v. CYC in NP lupus, with one small RCT favouring an i.v. CYC regimen over i.v. MP alone [186]. That trial used more CSs than we would recommend now and was based on a previous retrospective cohort study that suggested that i.v. CYC was useful in the management of NPSLE [371]. The RCT [186] recruited 32 SLE patients with active severe NP manifestations without thrombosis (such as seizures, optic neuritis, peripheral or cranial neuropathy, coma, brainstem disease or transverse myelitis) that had developed within the previous 15 days. All of the patients received oral prednisolone 1mg/kg/day for up to 3 months and then tapered depending on response and 1 g of i.v. MP daily for 3 days. One group received further 1 g of i.v. MP daily for 3 days repeated monthly for 4 months then bimonthly for 6 months and finally 3 monthly for one year. The other group received i.v. CYC 0.75g/m^2 body surface monthly for 12 months then this dose was repeated every 3 months for another year. The primary end point was at least 20% improvement from baseline using clinical, laboratory or specific neurological criteria and was met in 18/19 (95%) receiving CYC and 6/13 (46%) receiving MP [186]. A Cochrane systematic review of the treatment of NPSLE [372] calculated a relative risk of 2.05 (95% CI: 1.13, 3.73) for 20% response at 24 months with CYC therapy, but most patients responded by 5 months. CYC treatment was also associated with greater improvement in other lupus manifestations, a significant reduction in SLEDAI score at 6 and 12 months, greater reduction in prednisolone dosage and more patients completing the protocol compared with the MP group. There was no difference in adverse events, including infections and deaths. Recruitment to the study was stopped early due to the higher failure rate of the MP arm. Although the RCT is not of high quality [372] due to the small number of patients studied, the heterogeneity of the NP events, the variable outcome measures used for their assessment, and potential confounding by variable oral CS dosing, it is clear that the i.v. MP regimen was not sufficient and that CYC was better at controlling active NPSLE and preventing relapse.

Further evidence for the use of CYC in NPSLE comes from a previous open-label, controlled pilot study on the

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use of low-dose i.v. CYC, with a mean dose of 21 mg/day oral prednisone in 37 NPSLE patients, compared with oral prednisone alone in 23 patients (mean dose 21 mg/day) [187], and a cohort study [373] in which a low-dose regimen of i.v. CYC was used in 25 patients with NPSLE with benefit and a low risk of adverse events. A case series [328] found that treating 13 patients with lupus psychosis with oral prednisolone starting at 1 mg/kg/day for 8 weeks and oral CYC (1–2 mg/kg/day) for 6 months followed by oral AZA (1–2 mg/kg/day) led to improvement within a mean of 44 days and only one relapse with psychosis after 2 years; however, 23% developed other NP features and 38% had non-NP flares over the mean follow-up of 7 years. Anti-psychotic agents were used in nine patients for a mean of 6 months. Evidence for CYC and other treatments in neuro-ophthalmic manifestations of lupus have been reviewed in a systematic review [374], but the data on treatment is mostly based on case reports and small case series, for example cases with neuromyelitis optica treated with or without CYC [374].

In contrast to the studies assessing low-dose regimens, high-dose CYC has been studied as well in the hope of achieving better responses in severe lupus. An open-label, uncontrolled study [375] reported the initial safety and efficacy of high-dose CYC (50 mg/kg $\times$ 4 days) without stem cell transplantation in 14 patients with refractory moderate to severe SLE despite CSs and at least one immunosuppressant. A prospective RCT [188] was designed to compare the efficacy and safety of a widely used standard i.v. CYC regimen (monthly i.v. CYC at 750 mg/m^2 body surface area for 6 months, followed by 3 monthly i.v. CYC for 2 years) with this high-dose i.v. CYC regimen. Entry criteria included moderate-to-severe lupus with renal (22 patients), neurologic (14 patients) or other organ system involvement (11 patients). There was no evidence that response differed between the regimens, but non-responders to monthly i.v. CYC could be rescued with high-dose i.v. CYC. There was no difference in serious adverse events, infections, premature ovarian failure or deaths between the two groups. Leuprolide (a gonadotropin-releasing hormone analogue) was not used to protect against ovarian failure [376]. This should be considered with i.v. CYC moderate- and high-dose regimens [188], as amenorrhoea and ovarian failure are dose- and age-related adverse events of CYC [370, 377], but are rare with the European low-dose i.v. CYC regimen (500 mg 2-weekly for 3 months only) recommended for LN [24].

The remaining data [133] supporting the use of CYC for other serious non-renal manifestations of lupus are obtained predominantly from a variety of cohort studies, small case series and case reports, including 5 patients with systemic lupus vasculitis [378], 11 patients with myocarditis [379] and 5 patients with heart failure due to myocarditis [380]. There is one open-label RCT comparing i.v. CYC with enalapril for 6 months in the treatment of pulmonary hypertension, which showed greater benefit from CYC but an increased risk of infection and gastrointestinal side effects [189].

Conclusions

There is considerable evidence supporting the use of i.v. CYC to reduce disease activity and CS usage in severe lupus, for both renal and non-renal disease, including NPSLE. There is no evidence that CYC prevents chronic damage, and all regimens are teratogenic, but there is less risk with the Euro-Lupus regimen of adverse events (such gastrointestinal side effects, alopecia, infection, amenorrhoea and infertility due to ovarian failure) than with higher dose regimens [12, 16, 24, 25, 133, 372]. Overall, the LOE for the use of CYC in non-renal severe lupus, including NPSLE, from 1 systematic review including 29 studies and 1 systematic Cochrane review of NPSLE is 2++, and the GOR is B.

MMF in severe SLE

Summary

There is considerable evidence supporting the use of MMF in the management of LN, and this has been discussed in the Joint EULAR/ERA-EDTA recommendations for the management of adult and paediatric LN [24] (Table 3) and the ACR guidelines for screening, treatment and management of LN [25]. The mean SOA of all of the authors of this guideline with each of the main EULAR/ERA-EDTA recommendations for the management of LN is shown in Table 3. There is very little evidence for the use of MMF in NPSLE, but it is being used to reduce other types of moderate and severe non-renal lupus disease activity (Table 7), to prevent flare and for its steroid-sparing properties, as an alternative to CYC or AZA, especially in cases where inefficacy, drug intolerance and concerns about toxicity arose. It is not compatible with conception, pregnancy or breast-feeding [239].

Evidence

As mentioned in the section on moderate lupus, there is a systematic review of non-biologic immunosuppressants in non-renal SLE [133] that summarizes the data from 8 papers (covering 768 patients with moderate/severe lupus), which assessed the efficacy and safety of MMF in the treatment of non-renal SLE, including the ALMS RCT comparing the use of MMF with that of CYC as induction therapy for LN [159], and 7 cohort studies including 6 discussed above [162–166, 351] and an abstract that does not meet the criteria for this guideline.

Conclusions

Overall, the LOE for MMF in non-renal lupus from 2 systematic reviews, 2 open-label RCTs in LN and 7 cohort studies is 2++, and the GOR is B.

Rituximab in severe SLE

Summary

According to the NHS England Interim Commissioning Policy Statement for rituximab in SLE [267], rituximab may be considered in patients with severe or moderate SLE (BILAG system category A or $\geqslant$2B system scores, or SLEDAI $>$6) who fail treatment with MMF or CYC, either because of lack of effect or due to adverse events,

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providing they have already failed another immunosuppressant or it would be contra-indicated, or who require unacceptably high long-term CS dosing to control their lupus activity (see Fig. 1 flowchart for eligibility and response criteria).

Evidence

Clinical examples of severe lupus are shown in Table 7, and the evidence for rituximab is summarized in Table 2. The systematic reviews by Duxbury *et al.* [201] and Cobo-Ibáñez *et al.* [200] provide evidence supporting the use of rituximab for non-renal severe manifestations of lupus, such as NP involvement (5 cohort studies [381–385]), haematological manifestations (6 cohort studies [383, 385–389]) and at least 10 other cohort studies [382, 383, 385, 387, 390–395]). The data for improvement in NPSLE are still limited and uncontrolled, but showed 73–100% response in small numbers of patients. There is some evidence for improvement (50–100%) in mostly refractory lupus patients and idiopathic autoimmune thrombocytopenia and haemolytic anaemia. There are some specific reports on the use of rituximab in neuro-ophthalmological cases in a systematic review of these conditions [374], and pooled data from European cohorts [396] on the effects of rituximab in LN, as mentioned in the EULAR/ERA-EDTA recommendations for the management of adult and paediatric LN [24]. There are insufficient data to comment on other specific severe lupus manifestations at present, but rituximab is accepted as having steroid-sparing properties (three open-label studies [192, 193, 199]).

Conclusions

Overall, the LOE for rituximab from 3 systematic reviews and 30 studies, including 1RCT and 3 open-label trials for reducing lupus disease activity and for steroid-sparing properties, is 2+, and the GOR is C.

IVIG in severe SLE

Summary

IVIG has been used most in patients with refractory cytopaenias, thrombotic TTP and the catastrophic variant of APS. It can be used in pregnancy (but does not prevent heart block or fetal loss) and in patients with infection. It is rarely indicated as there is not much evidence for its use (Table 2).

Evidence

Much of the initial data are from case reports or small case series reporting treatment of acute events in small numbers of patients [223–226]. A systematic review and meta-analysis covering 3 controlled and 10 observational studies in SLE concluded that IVIG led to a reduction in SLE disease activity scores and a rise in complement levels in 31% of patients ($P = 0.001$, 95% CI: 22.1, 41.3) . There were insufficient data to assess response using other outcome measures, although serious adverse events were rare and mild [227]. The observational studies often did not report concomitant medication and used a variety of outcome measures and treatment regimens, as discussed below.

IVIG at a dose of 400 mg/kg/day for 5 consecutive days was used monthly for 6–24 months with some benefit in an open-label, uncontrolled trial with 12 refractory SLE patients [210]. Another open-label study [213] assessed 13 female SLE patients with a flare who received 0.4 g/kg body weight IVIG daily for 5 days. Short-term benefit was seen irrespective of concomitant therapy. IVIG–related adverse effects were mild and rare, and there was no worsening of renal function [213].

Low-dose IVIG was used to treat histologically confirmed cutaneous lupus in 12 patients starting with doses of 1 g/kg $\times$ 2, followed by 400 mg/kg monthly until disease remission or for 6 months [214]. Five patients showed complete or almost complete (>75%) clearing of their skin lesions, two had partial improvement (>50%) and three had poor responses (<50%). There were few side effects in this study, but renal patients were avoided because nephrotoxicity has been reported in other studies [397].

A retrospective chart review of 62 patients treated with low-dose IVIG (~0.5 g/kg) on average every 5 weeks for a mean of 6 courses showed a steady reduction in SLEDAI score over 8 months [215]. Patients with fever, rash, mucosal ulcers, pleurisy, pericarditis, urinary casts and urinary red cells responded in over 50% of cases, but only 30% of arthritis cases responded. Patients with thrombocytopenia, vasculitis and alopecia did not respond. Another group also found a disappointing response to IVIG in thrombocytopenia [216] in a retrospective analysis of 59 patients with immune-mediated severe thrombocytopenia, 44 of whom had definite lupus. A transient response to IVIG was reported in three patients with haemolytic anaemia in another study [217].

The effect of high-dose IVIG (30 g of sulfonated IVIG on days 1–4 and 21–24) in 12 mild to moderate active lupus patients [218] was only temporary in most patients. High-dose IVIG treatment in 17/20 (85%) SLE patients given 1–8 treatment courses consisting of 2 g/kg monthly given over 5 days [219] led to some improvement in arthritis, fever, thrombocytopenia and NP lupus [219]. A retrospective chart review of 17 patients (including 11 with SLE), with a mean follow-up of 30 months and long-term high-dose IVIG treatment monthly for 6 months then every 2–3 months [220], found that there was a significant reduction in the SLEDAI score with significant steroid-sparing effects, and remission was achieved in 12 patients [220].

A case–control study [221] compared 12 pregnant SLE patients with a history of recurrent spontaneous abortions who were on high-dose IVIG (0.5 g/kg every 3–33 weeks) with 12 similar patients treated with prednisolone and NSAIDs. Patients in the IVIG group stopped prednisolone ($n = 4$) and NSAIDs ($n = 9$). Disease activity decreased by the end of pregnancy ($P < 0.0001$) and there was a reduction in autoantibodies and normalization of complement levels in the IVIG group. Such improvements were not seen in the control group, and there were three fetal losses due to spontaneous abortion in this group compared with none in the IVIG group. However, other studies

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have not confirmed that IVIG can prevent fetal loss [239], and it is possible that NSAIDs contributed to fetal loss in the control group [240].

A multicentre, prospective, open-label study of pregnant women with anti-SSA/Ro antibodies in the mother and birth of a previous child with CHB/neonatal lupus rash was undertaken to determine whether IVIG (400 mg/kg) given every 3 weeks from weeks 12 to 24 of gestation could prevent the development of CHB [211]. CHB was detected at 19, 20 and 25 weeks in 3 babies at a stage when 20 mothers had completed the IVIG protocol before the trial was stopped. An additional child without CHB developed a transient rash consistent with neonatal lupus [211]. Another European prospective study showed similar results [212].

A large retrospective, single-centre cohort study was published by Camara in 2014 [222], which included 52 SLE patients with predominantly cutaneous, haematological, NP and cardiac manifestations who received at least one cycle of IVIG (400 mg/kg/day for 5 days). IVIG was given to 27 patients with infection and active lupus disease, and 17 (63%) patients showed some response. In 18 (69%) of 26 patients with refractory active disease without infection, some response was seen also. This study was too recent to be included in the comprehensive review on the use of IVIG in rheumatic diseases [228] that covered the case–control study in pregnancy by Perricone *et al.* [221], 4 prospective open-label studies [210, 213, 215, 218, 219], a retrospective cohort study [220] in lupus and a small RCT in LN not discussed here [228].

Conclusions

IVIG, particularly the high-dose regimen, can have some beneficial effects in the short term on disease activity, but has to be continued with intermittent courses for sustained benefit to be seen and only then has steroid-sparing properties. It has a low rate of adverse events in non-renal patients, but can cause nephrotoxicity, especially with pre-existing renal disease. The evidence supporting its use is weak compared with that of other treatments that are cheaper and easier to administer, so it should be reserved for patients in whom other treatments are contra-indicated or have failed. Overall, the LOE for IVIG in non-renal severe lupus from 2 systematic reviews (including a meta-analysis, 3 open-label trials, 10 cohort studies and 4 case series) is 2–, and the GOR is D.

Plasma exchange (plasmapharesis) for severe SLE

Summary

Plasma exchange in SLE has been used in small numbers of patients with conflicting results since the late 1970s. A systematic review was published while this paper was in preparation [238]. It is rarely indicated, because there is inadequate data to support its use except in thrombotic TTP (Table 2).

Evidence

The evidence supporting treatment with plasma exchange, which is expensive and often difficult to organize, remains poor except for thrombotic TTP [229, 398], the catastrophic variant of APS [238] and refractory neuropsychiatric, haematological and renal lupus [238]. Even for rapidly progressive glomerulonephritis, the evidence is limited [399].

Studies have shown that plasmapheresis can reduce immune complexes and anti-dsDNA antibodies, but there is a rapid rebound of complexes and antibodies to pre-treatment levels, as shown originally in 5/8 patients [230]. Marked improvement after plasma exchange was seen in 7/11 (64%) SLE patients in another study [231] lasting up to 3 years, but one (9%) patient with a severe relapse died, and plasma exchange was ineffective in 3 (27%) patients. In another small study of nine patients, 5 (56%) improved, 2 (22%) progressed to end-stage renal failure, and 2 (22%) died due to complications of severe SLE [232].

There was less support for the use of plasma exchange in SLE after a trial comparing plasma exchange in combination with CYC and CSs with standard therapy revealed no benefit from the plasma exchange for 40 patients with severe LN [400]. However, to avoid the rebound increase in autoantibodies after plasma exchange, a synchronized protocol was developed by the Lupus Plasmapharesis Study Group, consisting of plasmapheresis (3 $\times$ 60 ml/kg) followed by high-dose pulse CYC (36 mg/kg) then 6 months of oral immunosuppression. This treatment led to rapid improvement in disease activity in the initial 14 patients with various severe SLE manifestations, sufficient for immunosuppressants including CSs to be withdrawn in 12 (86%) patients at 6 months. Treatment-free clinical remission was sustained in 8 (57%) patients for a mean of 5.6 years [233]. However, there has been concern that improvements seen in this and 2 other uncontrolled studies [234, 235] with 23 patients may have been due to the concomitant immunosuppressants. It is notable that the Lupus Plasmapharesis Study Group never reported on the final disappointing results of a randomized international multicentre trial comparing their synchronized protocol [233] with the administration of pulse CYC alone.

The evidence for treating patients who have diffuse alveolar haemorrhage, thrombotic TTP or catastrophic APS with lupus is predominantly from case reports and small case series [229, 236, 237]. Given the high mortality in TTP in general, but especially with lupus [229, 398], it is essential that patients with TTP are referred early for plasma exchange and specialist care [398, 401]. Further details about the experience with and potential use of plasma exchange and immunoadsorption in lupus and APS, including LN, are covered by the systematic review [238].

Conclusions

There remains a need for further research to better define the patients who are most likely to benefit from plasma exchange, but in general they are considered to be those who have TTP, severe refractory disease or contra-indications to conventional treatment (such as pregnancy). Overall, the LOE for plasma exchange for the treatment of non-renal severe lupus from one systematic review and

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Table 8 Research priorities to improve the management of lupus patients

Analysis of the BILAG Biologics Register data is needed to assess the efficacy and safety of using rituximab for treating refractory lupus disease, administered according to the NHS England Interim Clinical Commissioning Policy Statement.
Analysis of the BILAG Biologics Register should also provide some data on the use of MMF in non-renal lupus patients; this is needed to support data from previous renal trials.
More research into stratified and personalised medicine and the cost-effectiveness of immunosuppressive drugs in lupus patients is warranted to help identify which drug will be most suitable for an individual.
Trials of immunosuppressive regimens and biologic therapies that will significantly reduce the need for CSs are needed in renal and non-renal lupus patients.
The cost-effectiveness and value of monitoring drug levels in order to improve adherence/compliance with drug therapy and improve the outcome in terms of reduced disease activity, damage and steroid usage should be investigated (e.g. for HCQ, MMF).
The role of IVIG and plasma exchange in the management of lupus patients requires further evaluation.
More data are required on the long-term outcome for children born to mothers with lupus who were exposed to drugs used pre-conception, while pregnant and/or while breast-feeding.

NHS: National Health Service.

nine studies is weak [3], and the GOR is D, but for TTP it is strongly recommended (grade B), as for non-lupus patients with TTP.

Applicability and utility

Implementation

Diagnosis and assessment of lupus can be difficult due to multisystem involvement and variable laboratory and serological test results. These guidelines will increase knowledge and raise the standard of care for patients with lupus. Only HCQ, CSs and belimumab are licensed treatments for lupus. The evidence for the treatment options discussed in this guideline, which reflect current best practice, has increased considerably in the last 10 years, although there is still relatively little evidence from high-quality RCTs. There should be no barriers to implementation, apart from limitations on the funding for rituximab and belimumab discussed in the relevant sections. The guidelines will be widely presented at local, regional and national meetings for health professionals and patients, carers and supporters of relevant charities.

Key standards of care

Lupus patients should be referred to a physician with experience in managing lupus who can confirm the diagnosis, assess the level of disease activity and provide advice on treatment and monitoring of the disease, its complications and side effects of therapy. Managing immunosuppressive therapies and their potential toxicities in patients with lupus can be a considerable challenge due to the risk of infection, difficulties with attribution of cytopenias to lupus or cytotoxic drugs, and difficulties in distinguishing manifestations of lupus disease activity from damage and co-morbid conditions. Input from a multidisciplinary team including nurse specialists and physiotherapists is usually required, and management may involve a variety of specialists, including rheumatologists, nephrologists, dermatologists, haematologists, cardiologists, chest physicians, neurologists, obstetricians, podiatrists and occupational therapists working as part of collaborative clinical networks involving regional specialist centres, local hospitals and GPs.

It is important to get patients to a low level of disease activity, if not remission, using HCQ, immunosuppressants and the least amount of CSs possible, in order to reduce cumulative damage from the disease and its treatment with CSs [71]. If drug treatment is not working within the expected time frame, it is important to consider adherence to treatment and adjusting the therapy to reduce the accumulation of chronic damage.

Patients need personalized advice, written information and education about the disease and its drug treatment from members of the multidisciplinary team, including specialist nurses and an individual to contact in the event of new symptoms. Additional topics covered should include sun avoidance, adequate vitamin D intake, weight control, exercise, not smoking and other measures to reduce atherosclerotic risk factors, as well as cancer screening, contraception and pregnancy planning when the disease is under good control on appropriate treatment for conception.

Future research agenda

There is a need for more evidence to support decision-making in the management of lupus patients. The guideline development group identified certain priorities for research into lupus to help address this issue, and these are shown in Table 8.

Mechanism for audit of the guideline

To assess compliance with these guidelines, an audit proforma is available on the British Society for Rheumatology website.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in these guidelines.

Disclosure statement: D.D.'C. has undertaken consultancies and received honoraria from GlaxoSmithKline/Human Genome Sciences and Roche, has been a member of the speakers' bureau for GlaxoSmithKline/Human Genome Sciences, Union Chimique Belge (UCB) and Eli Lilly and has received research grant support from Aspreva/Vifor

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Pharma. C.G. has undertaken consultancies and received honoraria from Bristol-Myers Squibb, Eli-Lilly, GlaxoSmithKline, MedImmune, Merck Serono, Parexel, Roche and UCB, has been a member of the speakers' bureau for GlaxoSmithKline, UCB and Lilly and has received research grant support from Aspreva/Vifor Pharma in the past and UCB currently. Y.N. has received funding to attend scientific meetings and received honoraria from UCB and GlaxoSmithKline. P.N. has received funding to attend scientific meetings and received honoraria from UCB. I.N.B. has undertaken consultancies and received honoraria from AstraZeneca, GlaxoSmithKline, MedImmune, Merck Serono, Pfizer, Roche and UCB, has been a member of the speakers' bureau for GlaxoSmithKline, UCB and Pfizer and has received research grant income from Genzyme Sanofi, GlaxoSmithKline, UCB and Roche. B.G. has received honoraria from Pfizer. M.K. has received funding to attend scientific meetings and honoraria from AstraZeneca, MedImmune, GlaxoSmithKline, INOVA Diagnostics and UCB. S.B. has received honoraria from Actelion INB to attend scientific meetings, has undertaken consultancies and received honoraria from AstraZeneca, GlaxoSmithKline, MedImmune, Merck Serono, Pfizer, Roche and UCB and has been a member of the speakers' bureau for GlaxoSmithKline, UCB and Pfizer. M.G. has received funding to support scientific meetings from Roche, Abbvie and Bristol-Myers Squibb. D.J. has received research grants, honoraria and consulting fees from Roche/Genentech, consulting fees from Boehringer Ingelheim, Chemocentryx, GlaxoSmithKline and Medimmune and is a Board member of Aurinia Pharmaceuticals. D.I. has consulted for Merck Serono, Eli Lilly, Celegene, UCB, XTLBio, Anthera and Baxalta; the honoraria received have been passed on to a local arthritis charity. L.L. has received research funding in grants/in kind from Roche and Genentech, has acted as an advisor to Genentech, Medimmune and Rigel and has received honoraria/travel grants from Genentech, Roche and UCB. K.S. received funding to attend a scientific meeting from Daiichi Sankyo. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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Anti rheumatic drugs

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RHEUMATOLOGY

Rheumatology 2017;56:865–868
doi:10.1093/rheumatology/kew479
Advance Access publication 27 February 2017

Guidelines

BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs

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Key words: rheumatic disease, DMARDs, safe prescribing, treatment monitoring, methotrexate, co-morbidity, drug toxicity, shared care.

Executive Summary

Scope and Purpose of the Guideline

Need for guideline

The mainstay of treatment for inflammatory rheumatic disease involves DMARDs. The last 30 years have seen enormous shifts in the use of DMARDs, with earlier initiation in disease course as well as combination strategies. Many of the drugs used have potential for harm as well as benefit. Appropriate screening prior to DMARD initiation, as well as vigilant monitoring during therapy, are required to minimize the risk of harm. This current guideline supersedes the previous 2008 BSR/BHPR guideline [1].

Objectives of guideline

The aim is to provide evidence-based recommendations, which do not imply a legal obligation, for clinicians to follow when prescribing synthetic, non-biologic, anti-rheumatic drugs commonly used in management of multi-system rheumatic conditions.

NICE has accredited the process used by the BSR to produce its guidance for the use of non-biologic DMARDs. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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Submitted 20 July 2016; revised version accepted 16 December 2016

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DMARDs covered by this guideline

The following DMARDs are covered in this guideline: apremilast, AZA, CSA, HCQ, LEF, mepacrine, MTX, Minocyline, MMF, sodium aurothiomalate/myocrisin (gold), SSZ and tacrolimus.

Target audience

The target audience is health professionals directly involved in managing patients with rheumatic disease in the UK, including rheumatologists, specialist nurses, pharmacists and general practitioners.

The areas the guideline does not cover

This guideline does not cover the indications for DMARD therapy or the use of biologic therapy and other selective non-biologic DMARDs (e.g. kinase inhibitors). The guideline also does not cover prescribing in relation to pregnancy because this is covered by an existing guideline [2, 3].

Key recommendations from the guideline

Specific questions were considered in relation to each drug. What baseline screening is needed prior to drug initiation? What impact does co-morbidity have for prescribers? What routine monitoring is needed? When should therapy be interrupted? Recommendations based on systematically reviewed evidence are given below. A description of evidence and full recommendations are given in the full guideline, available at *Rheumatology* online.

Generic Recommendations before Commencing any DMARD

(i) The decision to initiate DMARDs should be made in conjunction with the patient/carer and be supervised by an expert in the management of rheumatic diseases (GRADE 1B, 100%).
(ii) Patients should be provided with education about their treatment to promote self-management (GRADE 1B, 100%).
(iii) When appropriate, patients should be advised about the impact of DMARD therapy upon fertility, pregnancy and breastfeeding (GRADE 1B, 100%).
(iv) Baseline assessment should include height, weight, blood pressure and laboratory evaluation [full blood count (FBC), calculated glomerular filtration rate (GFR), alanine aminotransferase (ALT) and/or asparate aminotransferase (AST), albumin; GRADE 1C, 97%].
(v) Patients should be assessed for co-morbidities because these may influence DMARD choice, including evaluation for respiratory disease and screening for occult viral infection (GRADE 1C, 97%).
(vi) Vaccinations against pneumococcus and influenza are recommended (GRADE 1C, 97%).

Drug-specific Recommendations

(i) MTX: All patients should be co-prescribed folic acid supplementation at a minimal dose of 5 mg once weekly (GRADE 1B, 97%).
(ii) AZA: Patients should have baseline thiopurine methyltransferase (TPMT) status assessed (GRADE 1A, 97%).
(iii) HCQ: Patients should have baseline formal ophthalmic examination, ideally including objective retinal assessment for example using optical coherence tomography, within 1 year of commencing an antimalarial drug (GRADE 2C, 88%).

Prescribing DMARDs in Patients with known Co-morbidities

(i) Pre-existing lung disease is not a specific contraindication to DMARD therapy; however, caution is advised when using drugs associated with pneumonitis in patients with poor respiratory reserve (GRADE 1B, 95%).
(ii) In patients with deranged liver biochemistry, hepatotoxic DMARDs should be used with caution, with careful attention to trends in test results (GRADE 1C, 100%).
(iii) In patients with impaired liver synthetic function (e.g. cirrhosis), DMARD therapy should be used with extreme caution (GRADE 1C, 97%).
(iv) Patients with chronic viral hepatitis infection should be considered for anti-viral treatment prior to immunosuppressive DMARD initiation (GRADE 1B, 99%).
(v) DMARDs must be used with caution in chronic kidney disease, with appropriate dose reduction and increased frequency of monitoring (GRADE 1C, 97%).
(vi) Cardiovascular disease and prior malignancy are not considered contraindications to DMARD therapy (GRADE 1C, 95%).

Recommended DMARD Blood Monitoring Schedule when Starting or Adding a New DMARD

(i) Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks; then once on stable dose, monthly FBC, creatinine/calculated GFR, ALT and/or AST and albumin for 3 months; thereafter, FBC, creatinine/calculated GFR, ALT and/or AST and albumin at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity (GRADE 2B, 97%).
(ii) Dose increases should be monitored by FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks then revert to previous schedule (GRADE 2B, 97%).
(iii) Exceptions/additions to the monitoring schedule for specific DMARDs are included in Table 1 (GRADE 2B and C, 100%).

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Table 1 Summary of monitoring requirements

Drug	Laboratory monitoring	Other monitoring
Apremilast	No routine laboratory monitoring	None
AZA	Standard monitoring schedule[a]	None
Ciclosporin	Extend monthly monitoring longer term[b]	BP and glucose at each monitoring visit
Gold	Standard monitoring schedule[a]	Urinalysis for blood and protein prior to each dose
HCQ	No routine laboratory monitoring	Annual eye assessment (ideally including optical coherence tomography) if continued for >5 years
LEF	Standard monitoring schedule[a]	BP and weight at each monitoring visit
Mepacrine	No routine laboratory monitoring	None
MTX	Standard monitoring schedule[a]	None
MTX and LEF combined	Extend monthly monitoring longer term[b]	None
Minocycline	No routine laboratory monitoring	None
Mycophenolate	Standard monitoring schedule[a]	None
SSZ	Standard monitoring schedule for 12 months then no routine monitoring needed	None
Tacrolimus	Extend monthly monitoring longer term[b]	BP and glucose at each monitoring visit

[a]Standard monitoring as per recommendations I and II for DMARD blood monitoring schedule when starting or adding a new DMARD. [b]Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis. BP: blood pressure.

Perioperative DMARD Management

(i) Steroid exposure should be minimized prior to surgical procedures, and increases in steroid dose to prevent adrenal insufficiency are not routinely required (GRADE 2B, 95%).

(ii) DMARD therapy should not routinely be stopped in the perioperative period, although individualized decisions should be made for high-risk procedures (GRADE 2B, 95%).

Intercurrent Infections

(i) During a serious infection, MTX, LEF, SSZ, AZA, apremilast, MMF, CSA and tacrolimus should be temporarily discontinued until the patient has recovered from the infection (GRADE 1A–C, 97%).

Recommendations for Shared Care Agreements

(i) The prescriber has responsibility for ensuring patients are adhering to monitoring guidance (GRADE 1C, 97%).

(ii) When prescribing takes place in primary care, it should be supported by local written shared care agreements, highlighting responsibilities of each party (patient, secondary care, primary care; GRADE 1C, 97%).

(iii) Contact rheumatology team urgently and consider interruption in treatment if any of the following develop: white cell count $<3.5 \times 10^9$/l; mean cell volume >105 fL; neutrophils $<1.6 \times 10^9$/l; creatinine increase >30% over 12 months and/or calculated GFR <60 ml/min; unexplained eosinophilia $>0.5 \times 10^9$/l; ALT and/or AST >100 U/l; platelet count $<140 \times 10^9$/l; unexplained reduction in albumin <30 g/l (GRADE 1C, 99%).

As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g. gradual decreases in white blood cells or albumin, or increasing liver enzymes).

For clinically urgent abnormalities, emergency access to specialist rheumatology advice, with response within one working day, should be available as per National Institute for Health and Care Excellence guidelines.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: J.G. has received honoraria from MSD and Pfizer. J.M. has received honoraria from Bristol Myers Squibb and Pfizer. S.M. received honoraria from AbbVie, Pfizer, Roche and MSD. All other authors have declared no conflicts of interest.

Supplementary Data

The full guideline is available as supplementary data at *Rheumatology* Online.

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Clinical vignette

Rheumatology 2017;56:868
doi:10.1093/rheumatology/kew424
Advance Access publication 10 December 2016

Recognizing the clinical triad and dural calcification in adult hypophosphatasia

A 49-year old man who was treated for presumptive ankylosing spondylitis since adolescence presented with a 6 month history of thigh and knee pain. Clinically he had limited lumbar spine movement and patellar tenderness.

Laboratory indices revealed low serum alkaline phosphatase (17 U/l) but normal calcium, phosphate, parathyroid hormone, 25(OH)D and creatinine. HLA-B27 was negative and radiographic sacroiliitis was not present. Lumbosacral spine X-rays showed DISH-like changes (posterior longitudinal ligament calcification, paravertebral bridging, linear calcification and vertebral body hyperostosis). There were proximal right femur and bilateral patellae fractures. A CT scan of his lumbar spine showed spinal dural calcification (Fig. 1). Elevated urinary phosphoethanolamine (PEA; 47 μmol/mmol creatinine) confirmed the diagnosis of adult hypophosphatasia [1, 2]. A review of his family members revealed two siblings with chronic back pain, early loss of deciduous teeth, fragility fractures, low serum alkaline phosphatase, elevated urinary PEA and calcification of the posterior longitudinal ligaments.

A triad of low alkaline phosphatase, pathologic fractures and ectopic calcification should alert the physician to adult hypophosphatasia [1, 2]. In this case, the unusual finding of spinal dural calcification differentiated adult hypophosphatasia from other spine and metabolic bone diseases, thus aiding in diagnosis.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

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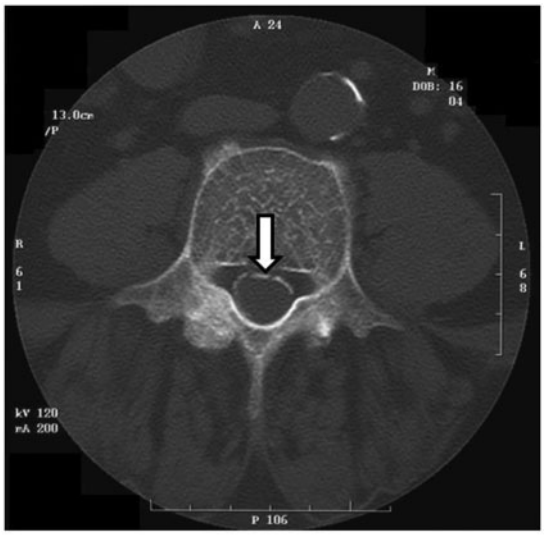
FIG. 1 CT of the lumbar spine showing diffuse calcification of the dura



CT of the lumbar spine showing diffuse calcification of the dura (arrow). The calcification does not lie in the posterior longitudinal ligament, as was originally seen on plain films (data not shown).

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RHEUMATOLOGY

Rheumatology 2019;58:e3–e42
doi:10.1093/rheumatology/key208
Advance Access publication 21 August 2018

Guidelines

British Society for Rheumatology

The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis

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Key words: rheumatoid arthritis, psoriatic arthritis, psoriatic arthritis, ankylosing spondylitis, biologic, Anti-TNF, safety

Introduction

The use of biologic therapies has transformed the management of inflammatory arthritis (IA). In contrast to conventional systemic DMARDs (csDMARDs) traditionally used to treat inflammatory disease, these agents offer a targeted approach, and their widespread use has resulted in disease remission becoming an increasingly achievable goal. Biologic therapies are not without potential risk, and hence it is important that clinicians are aware of these risks and ensure that appropriate precautions are taken to minimize them. Information on the safety of biologic therapies continues to be collected through national registries, clinical and cohort studies and case series and reports.

This guideline supersedes the previous BSR/BHPR anti-TNF [1], rituximab (RTX) [2] and tocilizumab (TCZ) [3] guidelines and has been developed in line with the BSR Guidelines Protocol.

Scope and purpose

Background and need for guideline

In 2001, The British Society of Rheumatology published its first guidelines on the safety of anti-TNF agents in RA. This was subsequently updated in 2005 [4], and most recently in 2010 [1]. These guidelines covered the indications and precautions for the use of anti-TNF agents, and the action that should be taken in the case of an adverse event. The initial guidelines focused on the then-available first generation anti-TNF drugs (infliximab (INF), etanercept (ETN) and adalimumab (ADA)) in RA. This was then expanded in the 2010 guideline to include the newer anti-TNF agents, golimumab and certolizumab. Separate guidelines covering the use and safety of RTX [2] and TCZ [3] in RA were published in 2011 and 2014, respectively.

NICE accredited
www.nice.org.uk/accreditation

NICE has accredited the process used by the BSR to produce its guidance on the safety of biologic DMARDs in inflammatory arthritis. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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Submitted 7 February 2018; revised version accepted 7 June 2018.

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The previous 2010 BSR/BHPR biologics safety guideline focused solely on anti-TNF inhibitors for RA. While most safety evidence, especially long-term observational data, exists for the first generation anti-TNF agents in RA, since the last guideline there has been significant new information from clinical studies regarding the safety of both anti-TNF agents and the newer non-TNF biologic DMARDs, both in RA and in other licensed IA indications. In light of this, the 2010 guideline working group lead, and a new guideline working group confirmed, the need for an updated guideline combining the wider spectrum of biological agents used at present across their multiple approved indications.

Objectives of guideline

The purpose of this guideline is to provide evidence-based recommendations for the safe use of biologic therapies in adults (aged >18 years). Although the majority of published safety data still concern the use of first-generation anti-TNF agents in RA, this guideline has been expanded from the previous to cover the safety aspects of all biologic therapies (approved by the National Institute for Health and Care Excellence (NICE) as of June 2016; Table 1) for the treatment of RA, PsA and axial spondyloarthritis (SpA) including AS [referred to as inflammatory arthritis (IA) henceforth]. Therapies approved by NICE after June 2016, such as secukinumab, sarilumab and the Janus kinase inhibitors, are not included.

This guideline highlights several specific safety areas including recommendations for baseline screening prior to initiation, recommendations for monitoring, the implications of co-morbid disease and ageing, vaccinations and the management of biologic therapies in specific situations such as infection, malignancy and the peri-operative window.

Biologic therapies covered by this guideline (in alphabetical order) are shown in Table 1. Individual drug Summary of Product Characteristics (SPCs) are available online at www.medicines.org.uk, and can be used alongside this guideline.

The following indications are covered by this guideline: RA, PsA and axial SpA, including AS.

Target audience

This guideline is aimed at secondary health care professionals who are involved in the management of patients with IA receiving biologic therapies. This may include rheumatologists, rheumatology specialist nurses and allied health professionals, specialist pharmacists, rheumatology speciality trainees and patients. General practitioners, physicians in other specialties and surgeons who manage patients treated with biologic therapies may also find this guideline useful.

Table 1 Biologic therapies covered by this guideline

Biological therapy	Abbreviation	Mechanism of action
Abatacept	ABA	CTLA4-Ig
Adalimumab	ADA	Anti-TNF α
Certolizumab pegol	CZB	Anti-TNF α
Etanercept	ETN	Anti-TNF α
Golimumab	GOL	Anti-TNF α
Infliximab	INF	Anti-TNF α
Rituximab	RTX	Anti-CD20
Tocilizumab	TCZ	Anti-IL-6 receptor
Ustekinumab	UST	Anti-IL-12/IL-23

The areas the guideline does not cover

This guideline does not cover specific indications for biologic therapy in IA; this has been described in national and international disease-specific recommendations, as well as NICE guidance (www.nice.org.uk).

The guideline does not cover the safety aspects of csDMARDs. This has been recently updated in the BSR/BHPR non-biologic DMARD guidelines [5]. The guideline does not cover the use of biologic therapy for conditions other than RA, axial SpA including AS and PsA, nor safety in individuals aged <18 years. The safety of biologics in the context of pregnancy and breastfeeding is not covered here; this has recently been covered in the BSR/BHPR Prescribing Drugs in Pregnancy guidelines [6]. Finally, the guideline does not specifically cover the safety of biosimilar preparations of branded biologics; until further clinical data are available, the safety recommendations we propose for originator biologics can be applied to their biosimilar counterparts. Patients should be made aware of the potential switch to biosimilar preparations. The requirement for brand name prescribing and entry of patients into registries is essential to ensure ongoing pharmacovigilance including the collection of long-term observational safety data in this area.

Stakeholder involvement

This guideline was commissioned by the BSR Standards, Guidelines and Audit Working Group. A Guideline Working group (GWG) was created, consisting of a chair, Dr Chris Holroyd, alongside representatives from relevant stakeholders (Table 2). In accordance with BSR policy, all members of the GWG made declarations of interest, which is available on the BSR website.

Involvement and affiliations of stakeholder groups

The GWG was composed of rheumatology consultants from various clinical backgrounds, rheumatology specialty trainees, rheumatology nurse specialists and a patient representative. All members contributed to the development of key questions on which to base the search strategy, guideline content, recommendations and strength of agreement (SOA).

Rigour of development

This guideline has been developed in line with BSR's guideline protocol. A comprehensive literature search was undertaken by two reviewers, using MEDLINE, Cochrane, PubMed and EMBASE databases with specific search terms (Table 3). The reference lists of retrieved articles were manually searched for additional papers

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TABLE 2 Names and affiliations of the Guideline working party

Name	Role	Affiliation
Christopher Holroyd	Chair Biologics GWG	University Hospital Southampton
Rakhi Seth	Consultant Rheumatologist	University Hospital Southampton
Marwan Bukhari	Consultant Rheumatologist	University Hospitals of Morecambe Bay NHS Foundation trust
Anshuman Malaviya	Consultant Rheumatologist	Mid Essex Hospitals NHS Trust
Claire Holmes	Specialty trainee	University Hospital Southampton
Elizabeth Curtis	Clinical Research Fellow	MRC Lifecourse epidemiology Unit, University of Southampton
Christopher Chan	Specialty trainee	University Hospital Southampton
Mohammed A Yusuf	Specialty trainee	Mid Essex Hospitals NHS Trust
Anna Litwic	Consultant Rheumatologist	Salisbury District Hospital
Susan Smolen	Rheumatology research nurse	Mid Essex Hospitals NHS Trust
Joanne Topliffe	Rheumatology research nurse	Mid Essex Hospitals NHS Trust
Sarah Bennett	Rheumatology nurse specialist	University Hospital Southampton
Jennifer Humphreys	NIHR Academic Clinical Lecturer in Rheumatology	Arthritis Research UK Centre for Epidemiology, University of Manchester
Muriel Green	Patient Representative	
Jo Ledingham	Consultant Rheumatologist	Queen Alexandra Hospital, Portsmouth

and these were included if appropriate. All searches were performed up to the end of June 2016. Abstracts from BSR, EULAR and ACR annual conferences up to and including EULAR 2016 were also included.

Two thousand eight hundred and sixty-nine articles were identified from the literature search; after removal of duplicates, 560 were eligible for detailed review. Two reviewers independently extracted information from relevant papers using data extraction tables. Only articles in the English language containing information on the safety of biologic therapies were included. Two hundred and eighty-nine articles were finally included in the guideline.

The guideline was developed and drafted via a series of telephone conference calls and face-to-face meetings, using the retrieved literature to underpin and facilitate discussions. Due to the breadth of the guideline, designated members of the GWG were divided into sub-groups to lead on specific sections of the guideline. One subgroup led the anti-TNF section, another the RTX and abatacept (ABA) section, and the third group led the TCZ and ustekinumab (UST) sections.

Grading the evidence

The GRADE method was used to assess the quality of evidence and the strength of recommendation [7]. Accompanying each recommendation in this guideline, in brackets, is the strength of recommendation, quality of evidence and SOA. Each subgroup produced GRADE scores for their sections, which was then distributed to and ratified by the entire GWG.

Strength of recommendation

Using GRADE, recommendations were categorized as either strong (denoted by 1) or weak (denoted by 2), according to the balance between benefits and risks. A strong recommendation was made when the benefits clearly outweigh the risks (or vice versa). A weak recommendation denotes that the benefits are more closely balanced with the risk or more uncertain.

Quality of evidence

Using the GRADE approach, the quality of evidence was determined as either high (A), moderate (B) or low/very low (C) reflecting the confidence in the estimates of benefits or harm.

High quality (A): typically generated from well-conducted meta-analyses, randomized controlled trials (RCTs) or other overwhelming evidence (such as large, well-executed observational studies with a low risk of bias). Further research is very unlikely to change confidence in the estimate of effect.

Moderate quality (B): usually from randomized controlled trails or observational studies with important limitations. Further research is likely to have an important impact on and may change the estimate of effect.

Low quality (C): usually from observational studies, or randomized controlled trials with major limitations. Further research is very likely to have an important impact on the confidence in the effect estimate and is likely to change the estimate. Very low quality evidence is usually derived from observational studies with serious limitations or from non-systematic observations (such as case reports and case series).

SOA

Each draft recommendation was evaluated by all members of the GWG. Based on the strength of recommendation and level of evidence, each recommendation was subject to a vote by all members of the GWG; a scale of 1 (no agreement) to 10 (complete agreement) was used. Only recommendations with a mean SOA score of $\geqslant 7$ plus $\geqslant 75\%$ respondents scoring $\geqslant 7$ were included. The SOA is presented next to the GRADE score for each

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Table 3 Search terms used for literature review

Topic	Search terms used in addition to either:
	'Rheumatoid + arthritis', 'Ankylosing spondylitis', 'Seronegative + arthritis', 'Psoriatic arthritis', 'Seronegative + spondyloarthropathy', 'Spondyloarthropathy'
	AND one of
	Abatacept
	Adalimumab
	Certolizumab
	Etanercept
	Golimumab
	Inflximab
	Rituximab
	Tocilizumab
	Ustekinumab
	TNF
	TNF inhibitor
	TNF agent
	Anti-TNF
	Non-anti-TNF
	Biologic*
Bacterial infection	Infec*
	Sepsis
	Septic
	Bacteria*
	Listeria
	Salmonella
	Campylobacter
	Escherichia coli
	E. Coli
	Bacillus cereus
	Staphylococc*
	Streptococc*
	Brucella
	Clostridium
	Pneumocystis
	PCP
Mycobacterial infection	Mycobacteri*
	Tuberculosis
	Mycobacterium
	MTB
	TB
HIV infection	HIV infect*
	AIDS
	Kaposi sarcoma
	Retroviral positive
Hepatitis	Hepatitis
Viral infection	Varicella
	Herpes
	EBV
	CMV
	HPV
	Cytomegalovirus
	Epstein Barr Virus
	HSV
	VZV
	Varicella
	Zoster
Fungal infection	Fung*
	Histoplasmos*
	Aspergillus
	Coccidiomycosis
Malignancy	Malignancy
	Pre-malignant
	Cancer
	Lymphoma
	Lung cancer
	Bowel cancer
	Non-melanoma skin cancer
	Tumour
	Tumor
	Carcinoma in situ OR CIS
	Cervical* OR CIN
	Barrett*
Heart failure	Heart failure
	Cardiac failure
Ischaemic heart disease	Ischaemic heart disease
	Ischemic heart disease
	Myocardial infarct*
	Coronary artery bypass graft
	NSTEMI
	STEMI
	Acute coronary syndrome
Respiratory disease	Interstitial lung disease
	Fibrosis
	Pulmonary fibrosis
Uveitis	Uveitis
	Drug induced uveitis
Demyelinating disease	Demyelinat*
	Neuro*
	Optic neuritis
	Multiple sclerosis
Diverticular disease	Diverticul*
Vaccinations	Vaccin*
	Vaccine
	Pneumococcal vacc*
	Influenza vacc*
	Singles vacc*
	Hepattiis vac*
Monitoring	Monitor*
	Test*
Connective tissue disease	Drug induced vasculitis
	Drug AND induced AND lupus
	Drug induced lupus
Haematological disorders	Anaemia
	Neutropenia
	Pancytopenia
	Aplastic anaemia
	Lymphopeni*
	Thrombocytopeni*
Psoriasis	Drug induced psoriasis
Peri-operative period	Postoperative infection
	Surgery + infection
Other terms	Elderly
	Geriatric*
	Care of the elderly
	Mortality
	Safety

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recommendation as a percentage (e.g. 100% would imply all responses were 10/10).

Limitations of this guideline

The literature search excluded any articles not available in English language and any non-human studies. In addition, there were a very small number of articles identified through the search strategy that we were unable to obtain through university library channels.

Plan for review

In line with BSR's guideline protocol, this guideline will be updated in 3–4 years, but if there is a significant change in the evidence base then an earlier update may be undertaken.

The guideline

To date, most long-term observational studies have focused on the safety of first generation anti-TNF agents (INF, ETN and ADA) in RA. In some areas, there is an increasing body of evidence regarding the safety of non-TNF biologic agents; however, there remains a paucity to guide many clinical scenarios. Where appropriate the evidence underpinning our recommendations has been divided into two sections: anti-TNF biologics and non-anti-TNF biologics.

Generic recommendations

(i) The decision to initiate a biologic should be made in conjunction with the patient/carer and initiated by an expert in the management of rheumatic disease (grade 1C; SOA 99%).

Biologic therapy for IA can be prescribed when patients meet the respective NICE recommendations. As NICE restrict eligibility and there are potential risks (as discussed through this document), as well as benefits from biologic therapies, decisions to initiate therapy should be made by a consultant rheumatologist. Following national initiatives and guidance, patients and/or their carers should be actively involved in the decision making processes.

(ii) Patients should be provided with education about their treatment to promote self-management (grade 1B, SOA 99%).

A Cochrane review in 2002 demonstrated that education had a positive effect in terms of both patient reported outcome and objective measures of clinical response; however, the benefits were not observed during a longer duration of follow-up [8]. The Department of Health has estimated that the average cost of education and self-management is £125/person and would save costs of £244/person on average [9].

Rheumatologists should therefore offer patients with IA the opportunity to discuss their condition and the risks and benefits of treatments both at diagnosis and throughout the course of their disease. Patients with IA should be offered verbal and written information to improve their understanding of their specific condition and its management. For those patients who would like further information, participation in existing educational activities including self-management programmes is recommended [10].

(iii) Patients should be assessed for co-morbidities as these may influence biologic choice, including evaluation for respiratory disease and screening for infection (grade 1C, SOA 99%).

Comorbid conditions such as respiratory disease and underlying infection have significant implications for both csDMARD and biologic prescribing. Patients should be assessed for such comorbidities at baseline and reviewed regularly (at their annual review and upon changes in treatment as a minimum). Further information is detailed later in this document.

(iv) Patients should have direct access to their specialist centre [e.g. via an advice line (Helpline)] for advice within one working day (grade 1C, SOA 98%).

The NICE quality standard (QS33) for the management of RA states that patients experiencing flares in their condition or a drug-related side effect should be offered, and be able to obtain, direct advice from their rheumatology service [11]. Advice should be available within one working day and when required prompt action should be taken to ensure patients' safety and optimize management of their RA. The principles behind this recommendation should also be applied to the other IA problems covered by this guideline.

(v) Clinicians should be encouraged to recruit patients to the appropriate biologic therapy registry, with patient consent (grade 1C, SOA 98%).

Although RCTs are considered the gold standard for the demonstration of biologic therapy efficacy, they are limited in their use for collecting safety data. There are several reasons for this—small patent numbers in RCTs make the detection of rare side effects difficult, short duration of follow-up leads to challenges in the detection of delayed side effects, homogeneous patient recruitment may not be representative of real life, exclusion criteria hamper recruitment of patients with important co-morbidities and RCTs are generally powered to detect efficacy outcomes, rather than significant safety signals. It is important that patients are recruited to the appropriate national biologic therapy registries [such as the British Society for Rheumatology Biologics Register for RA (BSRBR-RA) and the British Society for Rheumatology Biologics Register for AS (BSRBR-AS)], to enable long-term collection of real-life safety data on a large scale.

For patients prior to treatment with a biologic

Pre-treatment investigations

(i) Baseline assessment for all should include (grade 1C SOA 98%): laboratory evaluation of full blood count (FBC), creatinine/calculated glomerular filtration rate (GFR), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), albumin,

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tuberculin skin test (TST) or interferon-gamma release assay (IGRA) or both as appropriate, hepatitis B and C serology, and a chest radiograph.

Baseline assessment in both csDMARD and biologic prescribing acts as a screening tool for underlying conditions such as lung, renal or hepatic disease and also provides a reference point for future comparison. While the pick-up rate of routine investigations in a healthy individual is low, there is an increased incidence of significant abnormalities in RA patients, due to their increased overall burden of comorbidities [12]. Screening for TB and hepatitis are discussed in more detail in the mycobacterium tuberculosis and hepatitis sections.

(ii) Patients receiving RTX: baseline immunoglobulins (IgA, IgG and IgM) are recommended prior to initiation (grade 1A, SOA 98%).

Few patients would be expected to have low Ig levels before the start of RTX therapy: $\leqslant$2.2% in one study of 3595 patients [13]. However, several studies have found that a low level of immunoglobulins, especially IgG, is associated with a higher risk of neutropaenia and infection in patients receiving RTX [13–16].

(iii) Patients receiving TCZ: a baseline lipid profile is recommended prior to initiation. If abnormal, lipid lowering treatment should be initiated as per local guidance (grade 2A, SOA 99%).

Blockade of the IL-6 receptor by TCZ is associated with an increase in lipid parameters compared with baseline. Despite the increase in low-density lipoprotein (LDL)-cholesterol, trial data seem to indicate that the ratio of total cholesterol: high-density lipoprotein (HDL)-cholesterol remains unchanged [17]. A *post hoc* retrospective pooled analysis [18] of 3986 patients who received TCZ found 0.34 independently adjudicated major adverse cardiovascular events (MACE) per 100 patient-years in 24 weeks of follow-up. The study found an association between baseline total cholesterol: HDL-cholesterol ratio and MACE, with poor RA disease control associated with a higher risk of future MACE.

Pre-treatment management of and screening for co-morbidity

Infection. In general (recommendations for *Mycobacterium tuberculosis*, viral hepatitis and HIV are discussed separately):

(i) Biologics should not be initiated in the presence of serious active infections (defined as requiring intravenous antibiotics or hospitalization (grade 1B, SOA 98%).

Patients with RA, especially those with severe disease and extra-articular manifestations, have a higher risk of infection, estimated at double the risk of the general population [19]. Patients with severe disease, who already have a higher risk of infection, are more likely to receive biologic therapies; hence when evaluating the association between a drug and infection risk, it can be difficult to determine whether the infection risk is drug-related or is in keeping with that expected for the disease severity.

The most recent Cochrane review of 106 controlled trials, including 42 330 patients with RA, found that patients receiving standard dose biologic therapies were at a 27% higher odds of serious infection compared with controls [20], findings consistent with the same author's earlier Cochrane review [21].

Anti-TNF biologics. Of all the studies evaluating the safety of biologic therapies, those investigating the association between anti-TNF agents and infection risk are the most numerous, the majority of which have focused on the use of the first generation anti-TNF's (INF, ETN and ADA) in RA. Although there have been some inconsistencies between the results from various analyses, the majority of studies have found a significant association between anti-TNF drugs in patients with RA and a higher risk of serious infection.

Observational data from several national registries, including the BSRBR-RA [22], US Coronna registry [23] and the Spanish BIOBADASER 2.0 [24], have shown a significant positive association between anti-TNF agents and serious infection in RA. BSRBR-RA included data from 11 798 RA patients receiving ADA, ETN or INF, and 3598 csDMARD controls. The incidence of serious infection in the TNF group was 4.2/100 patient-years *vs* 3.2/100 patient-years in the DMARD group. The adjusted hazard ratio for serious infection in the TNF group was 1.2 (95% CI: 1.1–1.5) [22]; the highest risk of infection was in the first 6 months of treatment. This evidence has furthermore been supported by results from recent meta-analyses by Bernatsky *et al*. [25] and Michaud *et al*. [26], which both reported an approximate 1.4-fold increased risk of infection in RA patients treated with anti-TNF agents compared with csDMARD controls.

There is a relative paucity of long-term observational data investigating the risk of infection in other types of IA, such as AS and PsA. A Cochrane review [27] and a meta-analysis of RCTs [28] in AS, and two meta-analyses of RCTs in PsA [29, 30] found no elevated risk of serious infection with anti-TNF therapy used in these conditions; however, the analyses included a low number of RCTs compared with the RA data (between 6 and 21 studies) and event rates of infection were low making the studies underpowered to show a significant association. Given the theoretical risks, the advice substantiated by evidence for RA should be applied to patients with other IA problems.

Non-anti-TNF biologics. Comparatively fewer studies have examined the association between serious infection and non-anti-TNF biologic therapy. Longer term data on infection risk with these drugs is required, and until such information is available it would be prudent to take similar precautions with these drugs as with anti-TNF therapy.

With regards to RTX, the most recent observational data, from the US Coronna registry [31], showed similar rates of infection in 265 patients receiving RTX compared with 739 patients receiving anti-TNF therapy (event rate of 37.7 *vs* 41 events per 100 person-years). However, a previous RCT meta-analysis of the risk of infection with RTX

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[32], which analysed data from three studies, did not show an increased risk of serious infection in patients receiving RTX compared with placebo. An observational French study found that the risk was highest in the first 6 months after commencing treatment [14]. Long-term safety after 9 and 11.5 years was assessed and was deemed no higher than MTX and placebo [13, 33].

TCZ has been shown to increase the risk of serious infection in patients with RA. The risk is likely to be similar to anti-TNF therapy although long-term comparative data are not available. In the ADACTA study [17], which was a double-blinded parallel arm trial comparing the efficacy and safety of ADA and TCZ as monotherapy, the rates of serious infection were similar in both groups (3%). A systematic review by Campbell *et al*. [34] showed a slightly increased risk of infection with TCZ 8 mg/kg compared with controls, but similar to rates of infection with other biologics. Infection risk with the lower dose of 4 mg/kg was lower.

Yun *et al*. [35] conducted a retrospective cohort study using Medicare data including 23 784 patients on five anti-TNFs as well as ABA, RTX and TCZ, looking at incidence of hospitalized infection. The likelihood of being admitted to hospital with an infection on TCZ was lower than for INF, RTX and ETN, but higher than for ABA.

A study that pooled data from the double-blind and open-label phases of five clinical trials of s.c. ABA reported an incidence rate (IR) of serious infections of 1.79 (95% CI: 1.42, 2.24), which did not significantly change over time (mean exposure 27.3 months) [36]. This is in keeping with previous data for i.v. ABA [37]. A 2009 meta-analysis suggested that the risk of serious infections during ABA treatment [odds ratio (OR) = 1.35, 95% CI: 0.78, 2.32 *vs* placebo) is not significantly increased [32].

At present there is a lack of long-term observational data concerning the risk of serious infection with UST.

Given the theoretical risks with all biologics and the risk presented with the longer established treatments, the advice is that biologics should not be started in the presence of serious infection.

(ii) Use biologics with caution in patients at high infection risk after discussing risks and benefits (grade 1B, SOA 99%).

Several observational studies have identified factors that may increase an individual's risk of infection with biologic therapies. This additional risk may be unacceptable to patients, and needs to be carefully weighed up against the perceived benefits when prescribing biologic therapies.

Anti-TNF biologics. Comorbidities such as chronic obstructive pulmonary disease (COPD) [24, 38], interstitial lung disease (ILD) [24] and renal failure [24] have been associated with higher rates of serious infection in RA patients receiving anti-TNF agents. Concomitant steroid use has also been repeatedly associated with higher infection risk [24, 38]; however, in many patients the introduction of biologic therapies will enable reduction or cessation of steroid exposure. Although some studies have identified older age as an independent risk factor for serious infection with anti-TNF drugs, two recent studies have been reassuring. Data from BSRBR-RA showed that while older patients (aged >75 years) had a higher absolute risk of infection, there was no increased relative risk of serious infection on anti-TNF agents [22]. Similarly, no significant difference in serious infection rate was observed in a Swiss cohort of RA patients receiving anti-TNF therapy when divided into those above or below 65 years of age [39].

There is a lack of data concerning risk factors for serious infection in patients with other types of IA treated with anti-TNF therapy. Given the theoretical risks, the advice substantiated by evidence for RA should be applied to patients with other IA problems.

Non-anti-TNF biologics. The French AIR Registry, which analysed data from 1303 RTX-treated RA patients, found that rates of severe infection were significantly higher in those with chronic lung disease and/or cardiac insufficiency (OR = 3.0, 95% CI: 1.3, 7.3), extra-articular involvement (OR = 2.9, 95% CI: 1.3, 6.7) and low IgG level (<6 g/l) before initiation of RTX treatment (OR = 4.9, 95% CI: 1.6, 15.2) [14].

There is a lack of long-term observational data concerning risk factors for serious infection in patients with other types of IA treated with non-anti-TNF therapy; especially as UST is the only biologic within this category with a non-RA licence (for PsA). Given the theoretical risks, the advice substantiated by evidence for RA should be applied to patients with other IA problems.

(iii) Consider using ETN or ABA as a first-line biologic therapy in patients at high risk of infection (grade 2B, SOA 94%).

Anti-TNF biologics. There is some evidence from both RCTs and observational studies to suggest that the risk of serious infection may be lower with ETN compared with other anti-TNF agents. A meta-analysis of 44 RCTs found the odds of serious infection with anti-TNF agents to be lowest for ETN (pooled OR = 0.73, 95% CI: 0.45, 1.20 *vs* 1.42, 95% CI: 1.13, 178) for all anti-TNF agents combined) [26]. Several observational trials have also observed lower rates of serious infection with ETN, including a US claims database [40], BSRBR-RA [22], the Dutch DREAM registry [41], the Australian ARAD database [42] and the Italian GISEA registry [43].

Non-anti-TNF biologics. A low incidence of serious infection with ABA has been reported in long-term observational studies [36, 37] and a meta-analysis [44]. In the AMPLE study [45], an RCT comparing the safety and efficacy of s.c. ABA *vs* ADA in patients with RA over 2 years, numerically lower rates of infection were observed in the ABA arm (3.8%) compared with ADA (5.8%); however, this study was not powered to detect a significant difference in infection rates.

Mycobacterium tuberculosis

screening for TB before starting a biologic

(i) All patients require screening for tuberculosis (TB) before starting a biologic (grade 1B, SOA 98%).

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Anti-TNF biologics. The increased risk of active TB and reactivation of latent TB associated with anti-TNF treatment, as demonstrated in a number of studies, has led to a requirement to screen for active and latent TB in patients before anti-TNF treatment is given [46–54]. A 2014 meta-analysis of RCTs [55] confirmed an increased risk of mycobacterial infections in patients on biologics (OR = 3.73, 95% CI: 1.72, 8.13) and that the risk varied with different agents [see recommendation (iii) for latent and reactivated TB).

Non-anti-TNF- biologics. Relatively few large long-term studies have investigated the risk of TB reactivation with non-anti-TNF biologics. Although the results from studies appear reassuring for this group of drugs with regards to TB reactivation, until more data are available, the advice given for anti-TNF therapy should be considered.

Data regarding the risk of reactivating TB with RTX look reassuring. The largest study to date, which combined data from clinical trials and long-term extension studies, reported only two cases of pulmonary TB among 3595 RA patients who had received RTX over a mean follow-up of 11 years [12]. A Taiwanese study of 56 patients (43 patients were presumed to be without latent TB infection, seven patients had latent TB and six patients had anti-TNF-associated TB) found that over a 1 year period of RTX therapy, no patient developed active TB [56]. A 2014 review [57] found no cases of active TB recorded in patients with RA and other rheumatic conditions treated with RTX and ABA, and in fact, argued against pre-screening for TB in patients receiving these two biologics.

Koike *et al*. [58] published safety data from an all-patient post-marketing surveillance programme in Japan in 2011. Out of a total of 3881 patients treated with TCZ (1794 patient-years), four cases of active TB were identified (0.22/100 patient-years). Cantini *et al*. [57] observed eight cases of active TB in 21 trials of patients with RA receiving TCZ.

Combined data derived from five RCTs of s.c. ABA in RA found that TB occurred rarely, with an IR of 0.09 (95% CI: 0.04, 0.25) among 1879 patients [36]; this is lower than that observed for other biologics [59].

Regarding UST, a safety analysis of 3117 patients from five phase III clinical trials across the USA, Europe and Asia identified 167 patients with latent TB. These patients received isoniazid prophylaxis prior to receiving treatment with UST. No cases of active TB resulted in the 12-week treatment period. However, cases of TB have been reported in patients on UST [60].

(ii) Screening for TB should include checking for previous TB exposure and treatment, performing a clinical examination, chest X-ray (CXR) and either a TST or an IGRA or both, as appropriate (grade 2C, SOA 98%).

(iii) For patients on immunosuppressive therapy with a normal CXR, a TST is *not* helpful, as immunosuppression hinders interpretation (grade 2C, SOA 98%).

(iv) Patients with an abnormal CXR, previous history of TB or TB treatment should be referred to a specialist with an interest in TB prior to commencing a biologic (grade 2C, SOA 99%).

(v) Immunocompromised patients screened for latent TB with an IGRA alone or together with a TST and found to have a positive result in either test should be considered for treatment prior to starting biologic therapy (grade 2C, SOA 96%).

Investigations for latent TB infection in a person exposed to *M. tuberculosis* but without active signs of TB are based on the TST or IGRA.

The TST involves an intradermal injection of purified protein derivative and measurement of skin erythema and induration, which corresponds to a delayed-type hypersensitivity reaction in patients with previous exposure to TB (including latent TB). Previous vaccination with BCG will also cause a skin reaction but of a lower magnitude than after exposure to TB.

IFN-γ release assays [two commercially available: QuantiFERON-TB Gold In-Tube assay (QFT) and T-SPOT.TB] measure IFN-γ release by T cells in blood samples mixed with mycobacterium TB antigens. QFT measures the IFN-γ concentration (IU/ml) using ELISA technology, whereas T-SPOT.TB reports the number of T cells producing IFN-γ (spot forming cells). T-SPOT.TB is also known as the TB ELISPOT (enzyme-linked immunospot assay).

The TST and IGRA measure the response of T cells to TB antigens. As a false-negative result occurs in 20–25% of patients with active pulmonary TB, these tests should not be used alone to exclude a diagnosis of active TB.

Identifying latent TB in patients due to start biologic treatment has been problematic as the TST and, to a lesser extent, IGRA assays are thought to be less reliable in immunosuppressed patients [61, 62]. Most studies comparing TST with IGRA performance in immunosuppressed populations suggest sensitivity and specificity of IGRA is superior to TST [63–66] but not all studies support this [67, 68]. In addition, IGRA positivity has been shown to be more closely related to TB risk than positive TST results. A recent meta-analysis of the performance of the two available IGRA tests (QFT and T-SPOT.TB/ELISPOT) *vs* TST in patients with rheumatic disease before starting biologic therapy reported pooled concordances between the QFT assay and TST of 72% (65–78%) and between T-SPOT.TB and TST of 75% (67–83%). It also showed that IGRAs have a lower false-negative and false-positive rate, compared with TST, particularly in patients treated with corticosteroids and those with a history of BCG vaccination [69]. Although two IGRA tests are commercially available, based on the present data, there is no robust evidence to recommend a preference for one over the other.

The true sensitivity or specificity of the TST or IGRA is uncertain because a gold standard test for the presence of latent TB is currently unavailable. However, a closer correlation has been found between IGRA and risk factors for latent TB infection, including personal history, TB contact history and a suggestive CXR [65, 70]. Some studies have suggested using only an IGRA when screening for latent TB because in immunosuppressed patients, it is more specific than the TST and may therefore reduce the proportion of patients needing chemoprophylaxis

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[71, 72]. However, observational studies suggest that, given the discordance between these two types of test, use of one test may miss some patients with latent TB who would be identified by an alternative test [70, 73, 74]. Observational studies support the use of combination testing [61, 75].

Current international guidelines support screening all patients for latent TB before starting biologic therapy. However, given the inconclusive evidence available, the optimum screening strategy is unclear, with disagreement on whether to use an IGRA or TST, or both. In the UK, the 2016 guidance from NICE [76, 77] recommends testing all immunocompromised patients for latent TB with an IGRA alone or together with a TST—a positive result in either test should prompt consideration for treatment. However, the WHO recommends using either test and the European Centre for Disease prevention and control recommends using both [78, 79].

Screening with TST or IGRA is unhelpful in patients who have had treatment for active or latent TB. In this situation a chest X-ray and sputum examination will be sufficient, with input from a TB specialist.

Treatment of latent TB should be initiated after the possibility of TB disease has been excluded. The Centers for Disease Control and Prevention recommends treatment for latent TB in individuals with a positive IGRA result or a TST reaction of $\geqslant$5 mm, in immunosuppressed individuals (e.g. those on $>$15 mg/day of prednisolone for 1 month or longer and taking anti-TNFs), HIV-infected individuals, patients with organ transplants and individuals with fibrotic changes on CXR consistent with prior TB (cdc.gov/tb).

Treatment is also recommended in individuals with a positive IGRA or a TST reaction of $\geqslant$10 mm, including recent immigrants ($<$5 years) from high-prevalence countries, injection drug users and residents and employees in high-risk settings (e.g.: nursing homes and hospitals).

In addition, individuals with no known risk factors for TB may be considered for treatment of latent TB is they have a positive IGRA or a TST 15 mm or more. Targeted TB testing programmes are recommended among high-risk groups, with appropriate follow-up care.

The four treatment regimens for latent TB infection use isoniazid, rifapentine or rifampicin, and consultation with a TB expert is advised if the known source TB infection has drug-resistant TB.

TB drug treatment for the prevention of TB, also known as chemoprophylaxis, can reduce the risk of a first episode of active TB occurring in people with latent TB. Current evidence suggests that decisions about chemoprophylaxis should be based on the results of the TST and an IGRA. If either test is positive, it would be appropriate to treat with chemoprophylaxis while monitoring carefully for treatment-related side effects [76, 80, 81].

The majority of potential recipients of anti-TNF medication will have a normal CXR and will have been on immunosuppressive therapy thus hindering the interpretation of latent TB testing [82–84]. In these individuals, an individual risk–benefit calculation is recommended. If the annual risk of TB on anti-TNF treatment is higher than the risk of anti-TB therapy-induced hepatitis, then the risk–benefit analysis favours chemoprophylaxis; if lower, the risk–benefit calculation favours observation and investigation of symptoms [80]. The two chemoprophylaxis regimens commonly used in the UK are isoniazid for 6 months (6H) or rifampicin plus isoniazid for 3 months (3RH).

Latent and reactivated TB

(i) Patients should be treated with prophylactic anti-TB treatment prior to commencing a biologic (grade 1B, SOA 99%); therapy may be commenced after completing at least 1 month of anti-TB treatment and patients should be monitored every 3 months (grade 2C, SOA 91%).

(ii) Patients who have had previous inadequate treatment for active TB should be investigated for active TB. In these individuals even when active disease has been excluded, the annual risk of TB (reactivation) is much higher than the general population rate, so the risk–benefit analysis favours chemoprophylaxis (grade 1C, SOA 98%).

The above recommendation i and ii are based in part on expert opinion in the NICE guideline ‘Tuberculosis’ [76, 77] and the 2005 British Thoracic Society (BTS) guidelines [80]. While there is a consensus that all patients with latent TB should receive anti-TNF chemoprophylaxis prior to commencing a biologic, there is a lack of data regarding the point at which biologic therapy can then be started. The BTS guidelines suggest that a patient should receive a full course of anti-TB treatment before starting a biologic; however, while this is ideal, 3–6 months’ delay is likely to be unacceptable for the majority of patients due to the severity of their rheumatic disease. The BTS guidelines have not been updated since 2005, and since then clinical experience has developed. Current expert opinion suggests that biologic therapy can be started after competing at least 1 month of anti-TB therapy. This is primarily to ensure that anti-TB treatment is tolerated, especially in what is often a population over 55 years of age. Patients should be monitored every 3 months with close involvement with a TB specialist throughout.

Chemoprophylaxis for TB itself carries a small risk, with drug-induced hepatitis being the main issue, increasing with age and associated with increased mortality. It is important to exclude active TB disease before chemoprophylaxis is given, as there are concerns that single agent chemoprophylaxis given when active disease is present could lead to the development of drug resistance [67].

Two preventative treatment regimens in common use in the UK are isoniazid for 6 months (6H), or rifampicin plus isoniazid (3RH) for 3 months. Rifampicin and pyrazinamide for 2 months (2RZ) was a regimen used in the USA [85], but it had a very high rate of hepatitis with a number of fatalities reported [86]. Consequently, the choice of regimen is between 6H, which has a lower hepatitis rate, and 3RH, which is of shorter duration and with which there is thought to be better adherence and also less risk of drug resistance developing if active disease is present [87].

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(iii) As TB reactivation risk is higher with anti-TNF mAb drugs (notably ADA and INF) than for ETN, consider ETN in preference for those who require anti-TNF therapy and are at high risk of TB reactivation (grade 1B, SOA 99%).

The risk of TB reactivation appears higher with the mAb INF and ADA than for ETN [45, 46, 48–51, 53], a finding confirmed with registry data [47, 52]. In the BSRBR-RA the rate of TB was higher with ADA (144 events/100 000 person-years) and INF (136 events/100 000 person-years) than with ETN (39 events/100 000 person-years) [47]. After adjustment, the incidence-rate ratio (IRR) compared with the ETN-treated patients was 3.1 (95% CI: 1.0, 9.5) for INF and 4.2 (95% CI: 1.4, 12.4) for ADA. In light of this, we suggest that ETN should be considered as a first-line anti-TNF treatment in patients at high risk of reactivation of latent TB.

The incidence of TB for the newer anti-TNFs (certolizumab pegol (CZB) and golimumab (GOL)) is less well documented. Cantini *et al.* [57] assessed the safety data of both GOL and CZB in patients with rheumatic disease and identified 8 cases of active TB in 3387 patients with rheumatic disease treated with GOL (7 of the 8 TB cases occurred in TB-endemic countries, where the TB incidence is 50–299 cases per 100 000 inhabitants) and 10 cases of active TB in 3167 patients with RA treated with CZB.

Active TB

(i) Patients with evidence of active TB should be treated before starting a biologic (1C, SOA 99%); therapy may be commenced after completing at least 3 months of anti-TB treatment and there is evidence that the patient is improving with evidence of culture negativity (grade 2C, SOA 91%).

Full compliance with anti-TB treatment should be supervised by a thoracic physician or infectious disease specialist, and ideally continued until the drug susceptibility profile of the organism in those with positive cultures is known. Furthermore, it would be preferable to delay anti-TNF treatment until completion of a full course of anti-TB treatment (this is based on the expert opinion from the BTS [80]).

HBV and HCV

(i) Patients should be screened for hepatitis B and C viral infection (grade 1C, SOA 98%).

Hepatitis B and C are blood-borne infections of the liver that can result in chronic liver disease and hepatocellular carcinoma. NICE currently recommends that all people who are at increased risk of hepatitis B and C infection are offered testing and vaccination [NICE Public health guideline (PH43): Hepatitis B and C testing: people at risk of infection]. Examples of people at increased risk of hepatitis B and C infection are shown in Table 4.

For hepatitis B in particular, additional groups at increased risk include people who may have been exposed to sexually acquired infection.

For hepatitis C in particular, additional groups at increased risk include people who received a blood transfusion before 1991 or blood products before 1986, when screening of blood donors for hepatitis C infection and heat treatment for inactivation of viruses were introduced.

Screening for HBV should include HBsAg and antibodies to hepatitis B core antigen (anti-HBc) and surface antigen (anti-HBs), followed by HBV DNA test if HBsAg or anti-HBc are positive. These results will dictate the level of monitoring and prophylaxis, which varies between occult HBV infection (i.e. HBsAg negative and anti-HBc positive or anti-HBs positive) and overt HBV infection (i.e. HBsAg positive).

Screening for HCV infection is at present based on the detection of anti-HCV antibodies. If anti-HCV antibodies are detected, HCV RNA, or alternatively HCV core antigen if HCV RNA assays are not available, should be determined to identify patients with on-going infection.

The prevalence of hepatitis B and C as comorbidities in patients with RA varies across the world, due to epidemiological variations in risk factors. In a French cohort of patients with early RA, the seroprevalence of HBV and HCV infection was reported as 0.12 and 0.86%, respectively [88]. A higher seroprevalence of 3% for HBV and 2% for HCV infection was recently reported in COMORA, an international cross-sectional study of comorbidities in RA [12].

Acknowledging that there are now effective therapies for viral hepatitis, there is a strong rationale for offering screening to all patients prior to commencing immunosuppression.

(ii) In patients who are HBV positive, a risk–benefit assessment should be undertaken, as biologics may be safe if appropriate anti-viral treatment is given, working closely with a hepatologist (grade 1C, SOA 99%).

Anti-TNF biologics

There are a few medium-quality systematic reviews of observational studies evaluating the risk of reactivation of hepatitis B in patients with HBV infection treated with anti-TNF therapy in the context of an IA. A systematic review [89] included 536 patients with occult or overt HBV infection and an underlying rheumatological or dermatological condition treated with INF, ETN or ADA. The pooled estimate of HBV reactivation was 4.2% (95% CI: 1.4, 8.2%) for all patients. When the meta-analysis was restricted to patients with RA, the pooled prevalence of HBV reactivation was slightly lower at 3.3% (95% CI: 0.7, 7.5%). HBV reactivation rates were higher in the overt HBV group *vs* the occult HBV group (15.4 *vs* 3%). These reactivation rates were similar to those reported in two other systematic reviews [90, 91]. In a case–control study of RA patients with occult HBV infection [92], the use of anti-TNF therapy was more frequent in those with HBV reactivation than not (86 *vs* 36%) $P = 0.008$, hazard ratio (HR) = 10.9 (95% CI: 1.4, 87.7).

Patients who are HBsAg negative and anti-HBc positive (or anti-HBs positive) are nonetheless deemed to have an occult infection as low-level HBV replication may persist, with detectable HBV DNA in the liver but generally not in the serum. The clinical relevance of this is unclear

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Table 4 Risk factors for hepatitis B and C infection

People at higher risk of hepatitis B and C infection
People born or brought up in a country with an intermediate or high prevalence of chronic hepatitis B or C. This includes all countries in Africa, Asia, the Caribbean, Central and South America, eastern and southern Europe, the Middle East and the Pacific islands
People who have ever injected drugs
Men who have sex with men (particularly, HIV-positive men who have sex with men are at a greater risk of hepatitis C)
People in close contact with someone known to be chronically infected with hepatitis B or C
Prisoners, including young offenders

although immunosuppression may lead to HBV reactivation in these patients [93]. Therefore, where a decision is made to proceed with an anti-TNF agent on risk–benefit analysis, a rheumatologist should work closely with a hepatologist to ensure liver disease is fully assessed at baseline then monitored on treatment.

Several international groups have recommended that patents with overt HBV receiving immunosuppressive medicines should receive anti-viral prophylaxis [93, 94]. Perez-Alvarez *et al*. [95] found that of the reported cases of overt HBV patients treated with anti-TNF agents, HBV reactivation was 2.5-fold higher in patients not receiving prophylaxis (64 *vs* 26%). Of the 82 patients with overt HBV treated with an anti-TNF, five had acute liver failure, one required a liver transplant and four died. The European Association for the Study of the Liver suggest overt HBV candidates for immuno-suppressive therapy should be tested for HBV DNA levels and should receive pre-emptive anti-viral treatment during therapy (regardless of HBV DNA levels) and for 12 months after cessation of therapy. Occult HBV patients with detectable serum HBV should be treated like overt HBV patients [93].

Non-anti-TNF biologics

In patients receiving RTX, re-activation of HBV in patients with occult hepatitis B (HBsAg negative; anti-HBc positive) has been reported [96], with the authors suggesting that patients with sero-positivity for either occult or overt hepatitis B should be referred to a hepatologist.

A systematic review by Campbell *et al.* [34] found no increased risk of hepatitis B reactivation with TCZ; however, the number of cases was low and further long-term data are required. There are no data concerning the use of ABA and HBV.

There are very few published data on the use of UST in patients with chronic hepatitis B. In a small observational cohort of 14 with hepatitis B serology treated with UST, no increase in viral load was seen in patients who had received prophylaxis [97]. However, two out of seven patients (29%) who did not receive prophylactic anti-viral therapy were noted to have an increase in viral load. If clinically indicated, UST may be used in patients with hepatitis B following prophylactic anti-viral treatment.

In conclusion, given the theoretical risks and lack of high-quality data, we recommend that the recommendations supported by evidence for anti-TNF therapy should be applied to the non-anti-TNF biologics.

(iii) Studies to date suggest that though biologic therapy does not appear to have a detrimental effect on HCV infection, it should continue to be used only with caution in such patients, following a risk–benefit decision made with a hepatologist (grade 1C, SOA 96%).

There are limited data assessing the effect of immunosuppression on hepatitis C.

Anti-TNF biologics

A prospective RCT of 29 patients receiving ETN, MTX or both found that AST, ALT and HCV viral load did not significantly change across all three arms up to 54 weeks [98]. Three case series totalling 26 patients with IA and chronic HCV treated with either ETN, ABA or INF followed up to 36 months, did not show any significant increase in HCV titre over a 36-month follow-up [99–101]. One patient with both HBV and HCV had breakthrough HCV requiring treatment [99]. Studies to date continue to show that that anti-TNF therapy does not have a detrimental effect on HCV infection. Despite absence of high-quality evidence, in an era of advances in therapeutic options the advice remains to aim for viral control before immunosuppression.

Non-anti-TNF biologics

There is some evidence that the viral load of hepatitis C is increased after RTX treatment compared with anti-TNF therapy, but this was from a small study [96].

There are insufficient data to recommend the use of TCZ, ABA and UST in patients with chronic hepatitis C infection. A systematic review by Campbell *et al*. [34] showed no increased risk of hepatitis C reactivation with TCZ; however, the number of cases was low and further long-term data are required.

In a small observational cohort of four with hepatitis C serology treated with UST, no increase in viral load was seen in patients who had received prophylaxis [97].

HIV

(i) Risk factors for HIV infection should be documented prior to commencing a biologic and, if present, an HIV test should be performed (grade 2C, SOA 97%).

(ii) If considering the use of biologic therapy in HIV positive patients, this should be discussed with an HIV specialist. It should be borne in mind that a reasonable benefit to risk ratio for HIV patients

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exists with anti-TNF therapy if HIV infection is controlled ($CD4^+$ count >200 cells/mm^3 and viral load undetectable) and anti-TNF is given in combination with highly active anti-retroviral therapy (grade 2C, SOA 99%).

Individuals at risk of HIV are shown in Table 5. There is no evidence base to support the testing of all patients before commencing biologic therapy. The prevalence of HIV in most parts of the UK is low and the likelihood of a positive result in an individual without risk factors is very low. The recent NICE guideline NG60 [102] summarizes the groups in which an HIV test should be offered; it does not advise routine testing in all individuals prior to immunosuppressive agents, unless risk factors are present.

Anti-TNF biologics

The only evidence surrounding the use of anti-TNF therapies for IA in HIV-infected individuals comes from individual case reports and one case series. These reports suggest that they can be used to successfully treat IA in HIV positive patients and are generally well tolerated, provided that HIV treatment is well established prior to anti-TNF therapy initiation and CD4 count is >200 cells/mm^3.

The largest study to date is a retrospective case series of eight American HIV positive patients receiving either ETN, ADA and INF for rheumatic conditions [103]; five patients were receiving concomitant highly active anti-retroviral therapy (HAART). Anti-TNF therapy was restricted to those with CD4 cell count >200 cells/ml and viral loads of $<60\,000$ copies/ml at the initiation of the therapy Over a mean follow-up of 28.1 (range 2.2–55) months, anti-TNF therapy achieved good efficacy with no clinical adverse events attributed to anti-TNF treatment and no deterioration in CD4 count or viral load.

There have also been several individual case reports on the use of anti-TNF agents in HIV positive patients with co-existent rheumatic disease. Most patients receiving concomitant HAART had good clinical outcomes [104–106]; the sole exception is a case report of an HIV patient with PsA in whom ETN had to be stopped due to recurrent infections [107]. Although this patient was receiving HAART, his CD4 count was significantly lower than other cases (<50 cells/mm^3), which may explain the negative outcome.

Non-anti-TNF biologics

There is insufficient evidence to recommend the use of RTX, TCZ, ABA or UST in patients with HIV infection.

Malignancy

(i) Biologic therapies should not be commenced in patients with clinical signs of, or under investigation for, malignancy (basal cell carcinoma excluded) (grade 1C, SOA 96%).

(ii) Patients should be advised that there is no conclusive evidence for an increased risk of solid tumours or lymphoproliferative disease linked with biologic therapy, but that ongoing vigilance is required (grade 1A, SOA 99%).

Anti-TNF biologics: overall malignancy

There has long been concern regarding the possible association between biologic therapies and malignancy, indeed a 2006 meta-analysis of nine randomized controlled trials [108] found a 3-fold increase in the rate of malignancy with INF and ADA. Recent results from several further meta-analyses of both RCTs [26, 109–115] and observational studies [116, 117] have been reassuring and have failed to find a significant association between anti-TNF use and overall malignancy in patients with RA.

Most observational studies using national registry data have also been reassuring; recent studies from BSRBR-RA [118], BIOBADASER [119] and German RABBIT [120] registries have all failed to show a significant association between anti-TNF use in RA and overall malignancy, with up to 52 549 patient-years exposure. In contrast, studies using the Swedish ARTIS [121] and Danish DANBIO [122] registries have reported higher rates of invasive cervical cancer and colon cancer, respectively, in anti-TNF-treated RA individuals compared with those receiving csDMARD. Interestingly in the DANBIO study, when comparing the anti-TNF-treated RA group against the general population this association was no longer seen.

Few studies have looked separately at the AS and PsA anti-TNF-treated population with regard to malignancies. A 2009 meta-analysis of RCTs that included five PsA RCTs and 10 AS RCTs found no significant association [109]. Likewise, a study from BSRBR, which analysed data from

Table 5 Risk factors for HIV infection

Individuals at higher risk for HIV infection
Individuals from a country or group with a high rate of HIV infection
Men who disclose that they have sex with men, or are known to have sex with men, and have not had an HIV test in the previous year
Trans women who have sex with men and have not had an HIV test in the previous year
Individuals who report sexual contact (either abroad or in the UK) with someone from a country with a high rate of HIV
Individuals who disclose high-risk sexual practices
Individuals diagnosed with, or requests testing for, a sexually transmitted infection
Individuals who report a history of injecting drug use
Individuals who disclose that they are the sexual partner of someone known to be HIV positive or of someone at high risk of HIV (e.g. female sexual contacts of men who have sex with men)

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596 patients with PsA receiving anti-TNF and compared them with RF negative controls (as PsA patients not receiving anti-TNF are not included within this registry) found that the rates of new malignancies were not significantly different between the two groups [123].

Anti-TNF biologics: lymphoma

Patients with RA are known to be at an increased risk of lymphoma compared with the general population independent of treatment; reported risk ratios have varied from 1.9 to 2.7 compared with the general population [124, 125]. As this risk is likely to be highest in those patients with more severe disease, it is important that disease activity is considered as a confounder when assessing any relationship between anti-TNF use and lymphoma in this group. Current data do not suggest that PsA or AS are associated with an inherent increased risk of lymphoma [126–128].

Since the last published guideline in 2009, eight further studies have been identified, including one Cochrane meta-analysis [21], three further RCT meta-analyses [110, 115, 129], one meta-analysis of observational studies [116] and three cohort studies (using the French RATIO [130], Danish DANBIO [122] and Swedish ARTIS [131] registries). Although two of these studies found a higher risk of lymphoma in RA patients receiving anti-TNF agents compared with the general population [130, 131], reassuringly none of them found a significant difference between rates of lymphoma in RA patients receiving anti-TNF therapy compared with control RA patients.

Mariette *et al*. [130], in a cohort study using the French RATIO registry, found no increased risk of lymphoma in SpA patients receiving anti-TNF compared with the general population.

Non-anti-TNF biologics

There is much less long-term observational evidence evaluating the risk of malignancy with the non-anti-TNF biologics; however, findings to date have been reassuring. To date, there have been no safety signals for RTX, TCZ, ABA or UST in malignancy.

Although there is no direct evidence that RTX is safe in malignancy, most long-term data have not shown an increase in risk [13, 33]. Recent data from a pooled case analysis of 1246 patients receiving RTX for >5 years found no increase in the rates of malignancy compared with the general US population or compared with published data in adults with RA [13]. Similarly, data from a French cohort of 186 RA patients who had received at least one infusion of RTX did not show an increased risk of malignancy over 346 patient-years' exposure [mean follow-up 22.3 (15.1) months] [132].

A meta-analysis of 4009 patients exposed to TCZ for a median of 4 years found no significant difference in the incidence of solid and lymphoproliferative malignancies compared with the general population [133].

Solomon *et al*. [134], in a US observational study of 408 patients receiving ABA for RA, found no increased risk of malignancy compared with patients receiving MTX (HR = 1.55, 95% CI: 0.40, 5.97].

In a retrospective analysis of 3117 patients who received UST for up to 5 years, the rate of malignancy (other than non-melanoma skin cancers) was found to be 0.59/100 patients-years (UST 45 mg) and 0.61/100 patient-years (UST 90 mg) [60]. The frequency was found to be no different from the general population.

(iii) There is conflicting evidence regarding the risk of skin cancers with anti-TNF therapy; patients should be advised of the need for preventative skin care, skin surveillance and prompt reporting of new persistent skin lesions (grade 1B, SOA 96%).

Anti-TNF biologics

Although inconsistent, numerous studies have found a positive association between the use of anti-TNF agents in RA and the risk of malignant melanoma (MM). An observational study of US veterans with RA found a higher risk of MM in those exposed to anti-TNF agents compared with those receiving csDMARDs (HR = 1.5, 95% CI: 1.01, 2.24) [135]. An almost identical risk was observed in the Swedish ARTIS registry [136]. Other studies have also noted a positive association between anti-TNF agents and MM, but failed to reach statistical significance; these include the DANBIO registry [122] and a 2011 meta-analysis of observational studies [116]. The largest study to date combined data from 11 European registries including 48 304 RA anti-TNF-treated patients. One hundred and six invasive MM were observed in the anti-TNF group with a pooled standard incidence ratio of 1.2; however, this did not achieve statistical significance (95% CI: 0.99, 1.6; $P = 0.062$) [137]. Higher rates of MM were also observed in the TNF group compared with those receiving csDMARD; however, again statistical significance was not achieved (IRR = 1.14, 95% CI: 0.8, 1.6).

There is also some evidence to suggest that there may be a positive association between anti-TNF use and non-melanoma skin cancer (NMSC). Two RCT meta-analyses of RA patients receiving anti-TNF from 2009 to 2012 failed to find a significant association between anti-TNF use and risk of NMSC, although the more recent and higher quality of the two meta-analyses did observe a non-significant trend towards more NMSC in anti-TNF-treated patients [112, 115]. A further meta-analysis of observational studies found that patients with RA receiving anti-TNF had a 45% higher risk of NMSC compared with csDMARD-treated patients [116]. Recent registry data have also been conflicting; The ARTIS cohort [138] found higher rates of squamous cell skin carcinoma in RA patients treated with anti-TNF therapy compared with those who had not received anti-TNF therapy. While BSRBR-RA [139] and DANBIO [122] registries both observed higher rates of NMSC in anti-TNF-treated RA patients compared with the national population, no difference was observed when compared against RA patients who had not received anti-TNF agents.

Non-anti-TNF biologics

There is less evidence regarding the risk of NMSC in patients receiving non-anti-TNF biologics, but at present

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there have not been any safety signals to suggest that these drugs increase the risk of NMSC; however, further studies are required.

RTX and ABA were not associated with an increased risk of NMSC in a cohort of 6841 patients with RA receiving biologics in a Medicare cohort [140].

In a long-term safety analysis of 3117 patients with psoriasis receiving UST, the risk of developing NMSC was found to be 0.64 and 0.44/100 patient-years (UST 45 and 90 mg, respectively) [60], a similar rate to the general US population. However, we acknowledge that at a similar time point data in the anti-TNF cohorts were similarly inconclusive. As UST is a relatively new biologic drug, large-scale registry data are currently unavailable. We would therefore recommend that the same precautions outlined for anti-TNF agents be taken for UST.

(iv) Anti-TNF therapy is relatively contraindicated in patients who have had prior treatment with >150 psoralen and ultraviolet A (PUVA) and/or >350 ultraviolet B (UVB) phototherapy. Such patients should be discussed with a dermatologist prior to commencing anti-TNF therapy (grade 2C, SOA 96%).

Patients with a history of psoriasis may be at further increased risk of skin malignancy (in addition to that of anti-TNF therapy) due to previous phototherapy with UVB or PUVA [141].

Anti-TNF biologics

Data directly comparing the rates of skin malignancy in anti-TNF-treated patients with psoriasis who have received phototherapy compared with those who have never received phototherapy are lacking. A recent Dutch study compared rates of NMSC in two cohorts of patients receiving anti-TNF agents for psoriasis (99% of whom had received phototherapy) against a cohort of anti-TNF-treated RA patients [142]. A significantly higher risk of NMSC was found in the psoriasis group (HR = 6.0, 95% CI: 1.6, 22.4) with a shorter time to first NMSC compared with the RA group. A low basal cell carcinoma (BCC) to squamous cell carcinoma (SCC) ratio was also observed suggesting that disease-related factors, such as phototherapy, may be important contributors to the risk of development of NMSC in psoriasis patients treated with anti-TNF. However, the mortality associated with the majority of skin cancers is very low, early detection significantly improves both morbidity and mortality, and most are completely cured with local, predominantly surgical, measures.

Non-anti-TNF biologics

The limited available data from only a few studies do not suggest that any of the non-anti-TNF biologics increase the risk of skin malignancy. We suggest that while prior PUVA or phototherapy exposure is not necessarily a contraindication for this group of drugs, patients should be discussed with a dermatology specialist and treatment decisions made on a case by case basis.

(v) Caution should be exercised in the use of biologics in patients with previous malignancy (grade 1C, SOA 97%). The timing of commencement of biologic therapy post-malignancy is not fixed and will depend on type and stage of malignancy, risk of metastasis and patient views. RTX may be considered as a first-line biologic option in RA patients with previous malignancy (grade 2C, SOA 90%).

There remains a paucity of data concerning the use of biologic therapies in patients with a past history of malignancy. As RCTs have, almost universally, excluded patients with a past history of malignancy, any relevant data have been collected from observational cohort studies. Results from studies published since the last guideline have been reassuring; however, caution should still be advised based on theoretical risk and the fact that patient numbers and further event rates in these studies have generally been low.

Anti-TNF biologics

Of the recent observational cohort studies, BSRBR-RA included the largest number of patients, with 243 RA patients with previous malignancy receiving anti-TNF and 159 receiving csDMARD (1.7% of the BSRBR-RA cohort); the mean interval between malignancy and anti-TNF commencement was long at 11.5 years [143]. Fifty-three new malignancies were identified in this cohort, with no significant difference in the rate of new malignancies between groups. This is in keeping with previous data from the ARTIS [144] and RABBIT [120] registries. Furthermore, a 2016 systematic review observed similar rates of cancer recurrence in anti-TNF-treated individuals (which consisted of patients with RA, psoriasis and IBD) compared with the control csDMARD population (28.8 *vs* 35.1 events/1000 person-years) [145]. Additionally, these rates were also not significantly different from those observed in patients receiving no immunosuppressive therapy.

Two recent studies have looked specifically at the risk of recurrence of NMSC in patients receiving anti-TNF; results from these studies have been conflicting. BSRBR-RA found no increased risk of NMSC recurrence among 177 RA patients with a past history of NMSC receiving anti-TNF treatment compared with DMARD-treated patients, over a median follow-up of 4 years [139]. In contrast, a larger observational study of 6841 RA patients found that anti-TNF use increased the risk of a subsequent NMSC by 49% above that seen in RA patients treated with MTX alone [140].

There is a lack of data regarding the risk of malignancy recurrence in patients with PsA or AS treated with anti-TNF therapy.

Non-anti-TNF biologics

A small study from the BSRBR-RA followed up 23 patients with a prior malignancy who had received RTX as a first biologic for RA. Over a total follow-up time of 81 person-years, no increased rate of further malignancy was observed compared with csDMARD controls (unadjusted HR = 0.45, 95% CI: 0.11, 1.87). Similarly, RTX and ABA

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were not associated with an increased risk of a second NMSC in a Medicare cohort of 6841 patients with a history of NMSC receiving biologics for RA [140].

Data on the use of TCZ or UST in patients with a history of malignancy are lacking. Due to the theoretical risks, the advice substantiated by evidence for anti-TNF therapies should be applied to patients receiving these therapies.

(vi) The effect of biologics on pre-malignant conditions remains unclear. Caution should be exercised in the use of biologics in such patients. RTX may be considered as a first-line biologic option is these patients (grade 2C, SOA 97%).

Anti-TNF biologics

There is little information concerning the risk of using anti-TNF therapy in patients with pre-malignant conditions. Two studies to date have examined the risk of malignancy in female patients with a past history of cervical dysplasia or carcinoma *in situ* (CIS) of the cervix, treated with anti-TNF. The BSRBR-RA compared 190 RA patients with a past history of CIS of the cervix who were receiving anti-TNF therapy (73% of whom started anti-TNF therapy within 10 years of CIS) against csDMARD controls [146]. Over 893 person-years of follow-up, two new genital cancers were observed in the csDMARD group *vs* no new genital cancers in the anti-TNF group. Due to the low number of new malignant events in the trial, this study was underpowered to draw firm conclusions. Similarly, the DANBIO registry found no new genital malignancies among 208 patients with RA, AS or PsA and a past history of cervical dysplasia or CIS, who had been treated with anti-TNF therapy [147]. Limitations of this study included its relatively short follow-up period of mean 3.5 years for the anti-TNF patients, and the fact that the mean interval between CIS or cervical dysplasia diagnosis and commencement of anti-TNF therapy was 17.7 years. To date, no studies have examined the risk in other pre-malignant conditions such as Barrett's oesophagus or colonic polyps.

Non-anti-TNF biologics

To date, there are no data concerning the use of RTX, ABA, TCZ or UST in pre-malignant conditions. Overall, given the implications of malignancy and the relative lack of safety data in patients with an established or potential malignancy, biologics cannot be recommended at present.

Cardiac problems

(i) Although recent data are reassuring, biologics should be used with caution in patients with class III or IV cardiac failure, working closely with a cardiologist (grade 2C, SOA 96%).

Anti-TNF biologics

TNF-α levels are increased in the general population with heart failure [148] and experimental models have suggested that anti-TNF therapy may improve ventricular dysfunction [149]. However, early clinical trials of ETN and IFX used as a treatment of heart failure reported an increased risk of worsening chronic heart failure [150–152]. As a result the presence of a class III or IV heart failure was a contraindication to the use of anti-TNF therapy in RA (Table 6) [1]. Recently, an observational study compared 8656 patients starting treatment with traditional DMARDs with 11 587 starting an anti-TNF therapy and reported that anti-TNF therapy was not associated with an increased risk of hospital admissions due to cardiac failure compared with traditional csDMARDs [153]. Furthermore, in a recent systematic review and meta-analysis, no significant effect of treatment with TNF inhibitors on CF was observed in RA patients [154]. Interpretation of the results from these studies is hampered by issues relating to potential confounding by indication or contraindication and by lack of control for confounding conditions or severity of RA.

Non-anti-TNF biologics

At present, there are no safety signals to suggest that RTX is associated with deterioration of cardiac function. A pooled case analysis of 1246 patients receiving RTX for >5 years found no difference in cardiac events compared with the general RA population [13].

Studies have shown that IL-6 is associated with exacerbation of ischaemic heart disease and cardiomyopathy [155]. Suzuki *et al*. [156] used i.v. TCZ in a patient with severe RA, with triple vessel coronary artery disease and severely impaired left ventricular function, with no worsening of cardiac function but good results for RA control. There is currently no evidence to suggest that TCZ increases the risk of cardiac failure. However, as with all other biologic clinical trials, patients with moderate to severe heart failure were

Table 6 New York Heart Association classification of heart failure

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation or dyspnoea
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

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excluded from the studies and so the risk of biologic therapy in such patients has to be weighed against the potential risk of alternative therapies (such as steroids).

There are no data to suggest that ABA or UST is associated with exacerbation of cardiac failure.

(ii) Biological therapy may be used in patients with previous myocardial infarction or cardiovascular (CV) events (grade 2B, SOA 99%).

Data thus far appear to be reassuring with a potential beneficial effect of anti-TNF therapy on the risk of MI. Recently, a cohort study linking the Swedish National Patient Register and the Swedish Biologics Register [157] compared 7704 RA patients receiving anti-TNF therapy to matched biologic-naïve RA patients at a 3:1 ratio ($n = 23\,112$). There was a significantly lower risk for acute coronary syndrome among RA patients, who were exposed to anti-TNF therapy compared with the biologic naïve patients (HR = 0.82, 95% CI: 0.70, 0.95). This is consistent with the results of a systematic review and meta-analysis that found that anti-TNF therapy in patients with RA was significantly associated with a reduction in the risk of MI [154]. Data from the BSRBR-RA showed no significant difference in the incidence of first MI between RA patients taking TNF inhibitors and csDMARD-treated RA controls [158]. However, the subgroup of anti-TNF-treated patients with a good or moderate EULAR response at 6 months had a lower incidence of MI (3.5/1000 events in responders compared with 9.4/1000 events in non-responders).

Similarly, there appears to be a potential beneficial effect of anti-TNF therapy on CV events but further data are required before firm conclusions can be drawn. Potential confounding by indication or contraindication and by lack of control for confounding conditions or severity of RA should be taken into account, but this would be compatible with the hypothesis that inflammation contributes to development of CV events. In a recent systematic review and meta-analysis, in RA TNF inhibitors were significantly associated with a reduction in the risk of all CV events (risk ratio (RR) = 0.70, 95% CI: 0.54, 0.90), as well as in myocardial infarctions (RR = 0.59, 95% CI: 0.36, 0.97), strokes (RR = 0.57, 95% CI: 0.35, 0.92) and major adverse cardiac events (RR = 0.3, 95% CI: 0.15, 0.57) [154].

There is a lack of data regarding the use of anti-TNF therapy in patients with PsA or AS in patients with previous myocardial infarction or CV events.

Non-anti-TNF biologics

No data exist to suggest that any of the non-anti-TNF biologics increase the risk of myocardial infarction or CV events. In view of the evidence from anti-TNF therapies and a lack of a mechanistic reason, we suggest that the recommendation be applied across biologic therapies.

Respiratory disease

(i) Pre-existing ILD is not a specific contraindication to biologic therapy; however, caution is advised in patients with poor respiratory reserve (in whom a significant drop in lung function would be potentially life threatening); in this situation it is advised to work closely with a respiratory physician with a specialist interest in ILD (grade 2C, SOA 99%).

(ii) RTX or ABA may be considered a first-line biologic in patients with ILD (grade 2C, SOA 84%).

ILD is a common manifestation in patients with RA (prevalence 10–30%) and is generally associated with more severe disease [159, 160]. Uncertainty remains surrounding the natural history of RA-ILD and the effects of biologics (and csDMARDs) on this disease. Predominantly studies are centred on RA-ILD although there are pulmonary manifestations associated with other forms of IA, such as a prevalence of 0–30% for lung involvement in AS patients, most commonly upper lobe fibrosis.

Anti-TNF biologics

Since the 2010 guideline there have been several observational retrospective cohort studies assessing the relationship between ILD and anti-TNF therapy. The BSRBR-RA found no significant increase in mortality in 356 patients with RA-ILD treated with ETN, ADA or IFX, compared with those receiving csDMARD alone [161]. Selection bias could be an explanation for these results as this could have led to increased mortality in the traditional DMARD group and a favourable reduction in the mortality rate ratio for biologics use. The conclusion was that UK physicians were appropriately selecting patients suitable for anti-TNF therapy when underlying ILD was present.

Where there is no pre-existing ILD, a US study found that anti-TNF therapy was not associated with a diagnosis of ILD among patients with RA over a mean follow-up of 3 years [162]; comparisons across anti-TNF agents found no differences in risk. The number of cases was limited in this study, with only 38 new ILD cases (23 on anti-TNF) among the 8417 persons included (0.4%).

In terms of selection of patients, univariate analysis in a small Korean study suggested age at initiation of anti-TNF therapy was a risk factor for death when looking at a population of 24 RA-ILD patients on anti-TNF (76 *vs* 64 years old, $P = 0.043$) [163]. A Japanese study [164] found that over 1 year of follow-up of 58 RA patients with pre-existing ILD, 14 had ILD events and that the proportion was greater than the comparator arm without pre-existing ILD (24 *vs* 3%, $P < 0.001$).

Pre-existing lung disease should not be considered an absolute contraindication to an anti-TNF. However, in patients with poor respiratory reserve (in whom a significant drop in lung function would be potentially life threatening), caution should be exercised when choosing an anti-TNF. Decisions should be made on an individualized basis in conjunction with a respiratory physician, and with full appreciation of the limited evidence base.

Non-anti-TNF biologics

There is little evidence on the impact of RTX, ABA, TCZ and UST on the occurrence or exacerbation of ILD, and this is often limited to case reports.

A 2014 systematic review of case reports and series (from 1975 to 2013) of biologics causing ILD or worsening

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pre-existing ILD in RA patients found eight case reports for TCZ, three for RTX and one for ABA [165].

A US database study of 11 219 RA patients [166] found the lowest IR of ILD occurrence was with ABA (IR = 4.0/1000 person-years, 95% CI: 1.6, 8.2/1000 person-years); the highest being with INF (IR = 12.2/1000 person-years, 95% CI: 5.6, 23.2/1000 person-years); however, no significant differences in the incidence of ILD was found between the different biologic classes. No studies to date have examined the relationship between UST and ILD in PsA.

Until further data are available concerning any causal relationship between non-anti-TNF biologics and ILD, we suggest that recommendations given for anti-TNF therapies should be followed. There is a weak evidence base to suggest that ABA and RTX might have less effect on ILD than other biologics [165–167].

Uveitis

(i) ADA and INF can be considered for the treatment of uveitis, in preference to ETN, which appears to be associated with lower rates of treatment success and has been associated with the development of uveitis. The relative risks of these agents should be taken into account when selecting which treatment to use (grade 1 C, SOA 96%).

Anti-TNF biologics

A systematic review by Levy [168, 169] concluded that ADA and INF can be considered as second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior uveitis, panuveitis, severe uveitis associated with seronegative spondyloarthropathy and scleritis in patients requiring immunomodulation who have failed or who are not candidates for antimetabolite or calcineurin inhibitor immunomodulation. INF and ADA can be considered in these patients in preference to ETN, which appears to be associated with lower rates of treatment success. At present, ADA is the only anti-TNF agent licensed by the European Medicines Agency for the treatment of uveitis.

While ADA and INF [168, 169] have successfully treated uveitis, there are several case reports of uveitis developing in patients treated with ETN [170, 171]. A registry-based study by Lim *et al*. [172] reported 43 cases of uveitis in patients who were receiving anti-TNF treatment over a period of 8 years. The number of patients taking ETN, INF or ADA in this group was 20, four and two, respectively; ETN therapy was associated with a significantly greater number of reported uveitis cases in comparison with INF ($P < 0.001$). This study was, however, limited by the information on the clinical diagnoses available to the authors.

More data are required on uveitis associated with each of the anti-TNF agents before further conclusions can be drawn on the risks associated with these agents.

Non-anti-TNF biologics

There is a paucity of data concerning the safety of non-anti-TNF biologics in patients with a history of uveitis. There is one case report of a patient with RA treated with TCZ who developed acute anterior uveitis 5 weeks after stopping the therapy; however, causality is difficult to establish in this scenario [173]. Aside from that, there have not been any safety signals to suggest that there is concern about using these drugs in this patient cohort.

There is some, mostly observational, data to suggest that non-anti-TNF biologics can successfully treat patients with refractory uveitis. A systematic review by Simonini *et al*. identified nine articles reporting data on the use of non-anti-TNF biologics to treat refractory uveitis (six retrospective chart reviews, two case series and one single-blind RCT of 16 patients) [174]. ABA, TOC and RTX all demonstrated efficacy in selected categories of chronic uveitis, refractory to previous DMARDs and anti-TNF agents; further randomized clinical trials in this area are needed.

Demyelinating disease

(i) Anti-TNF therapy should not be given when there is a personal history of multiple sclerosis or other demyelinating diseases. Consider using a non-anti-TNF biologic in this situation (grade 2B, SOA 97%).

Anti-TNF biologics

Studies have suggested an aetiological role for anti-TNF therapies in the development of neurological disorders; the disease is temporally associated with initiation of therapy, the symptomatology is suggestive of an antigen-mediated hypersensitivity process, and the disease improves or resolves after discontinuation of therapy and a positive rechallenge phenomenon is observed [175, 176].

Multiple sclerosis

TNF blockade was shown to cause worsening of demyelinating disease in early studies of an anti-TNF therapy, in which patients with active multiple sclerosis (MS) documented an increase in MS flares on this therapy [177]. The prevalence of demyelinating disease induced by biologic therapies, reported in RCTs and post-marketing studies, has been estimated to range from 0.02 to 0.2% [178]. In a Canadian database of 105 000 RA patients there was a trend towards around a 30% increase in demyelinating events after exposure to anti-TNF agents, but this was not statistically significant [179]. A Danish registry study of almost 28 000 patients with IA found a significantly increased standardized incidence ratio of MS in men with RA or AS treated with anti-TNF therapy (SIR = 3.48, 95% CI: 1.45, 8.37), but not in women [180].

Optic neuritis

Case reports of patients developing optic neuritis during anti-TNF treatment exist. A pooled case report study detailed 15 patients who developed optic neuritis while on anti-TNF therapy; eight of these patients had received IFX, five ETN and two ADA [181]. On stopping anti-TNF treatment, seven patients experienced either partial or complete resolution of their symptoms while four patients continued to have symptoms. Recently there has been a USA-based study of 61 000 individuals with inflammatory disease and new anti-TNF or non-biologic DMARD use.

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Among this cohort, three optic neuritis cases (two with IFX and one with ETN) were detected among anti-TNF new users, providing a crude IR of 10.4 (95% CI: 3.3, 32.2) cases per 100 000 person-years. No cases occurred in the csDMARD comparison group. However, in a secondary analysis of current and past users of csDMARDs and anti-TNF, optic neuritis rates were similar in the anti-TNF and comparison groups, respectively, leading the authors to conclude that anti-TNF therapy does not appear to promote the development of optic neuritis in patients who lacked a prior documented history of optic neuritis [182].

Demyelinating peripheral nervous system disease

The association between anti-TNF treatment and various disorders of peripheral nerves such as Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy and mononeuropathy multiplex has been highlighted in various case series and case reports [183]. Cases were reported for all three first generation anti-TNF agents with symptoms developing over a wide range of time intervals from starting anti-TNF treatment (8 h to 2 years) and lasting for varying time periods from 3 weeks to 35 months. Withdrawal of anti-TNF resulted in slow resolution of symptoms in many cases; however, additional treatment was required for others. A small minority of patients, however, never achieved symptom resolution.

Prognosis following demyelinating disease or peripheral neuropathy

In the BIOGEAS registry, 30% of patients with demyelinating disease ($n = 44$) had no resolution of symptoms. Eleven per cent of peripheral neuropathies had no resolution of symptoms on stopping therapy [175, 178]. Similarly, in a French registry, 22% of patients developing CNS demyelination on biologics went on to develop MS despite cessation of biologic therapy [184].

In light of these findings, individuals with a personal history of multiple sclerosis or other demyelinating diseases should not start anti-TNF therapy.

Non-anti-TNF biologics

There is no evidence to suggest that RTX, ABA or UST increases the risk of demyelinating diseases. Likewise, there is no consistent evidence to argue against the use of TCZ in demyelinating diseases; indeed there is ongoing interest in its use for the treatment of certain autoimmune neurological disorders such as neuromyelitis optica spectrum disorder [185]. Sato *et al*. [186] used TCZ in treating RA in a patient with multiple sclerosis for 5 years with no progression of her MS.

In view of the above evidence, we suggest that a non-anti-TNF biologic is used in preference to anti-TNF therapy in patients with a personal history of demyelinating disorder.

Diverticular disease

(i) Exercise caution with TCZ in patients with diverticular disease, particularly when using concurrent NSAIDs and/or steroids (grade 2C, SOA 98%).

Gastrointestinal perforation has been reported in patients treated with TCZ for RA. An occurrence of 2.8/1000 person-years was reported by Schiff *et al*. [187] in a pooled meta-analysis of five RCTs and two long-term extension studies, compared with 2.0/1000 person-years reported in the control group. Diverticulitis was present in 16 of the 18 patients who had a gastrointestinal (GI) perforation while receiving TCZ; most patients had also been treated with NSAIDs and/or steroids.

A systematic review by Gout *et al*. [188] found that the risk of GI perforation with TCZ was lower than the risk with steroid and NSAID use, but higher than with anti-TNF therapy.

A large study by Curtis *et al*. [189] looking at administrative data from a large US health plan showed that there was no increased risk of GI perforation with the use of non-TCZ biologics or MTX, but there was an increased risk with concomitant use of steroids and NSAIDs. The factor leading to the highest increase in risk was previous diverticulitis.

Vaccinations

(Also refer to vaccination recommendations while on biologic therapy).

(i) HBV immunization should be considered for at risk patients (grade 2C, SOA 94%).

Individuals with ongoing risk factors for hepatitis B infection [as outlined in recommendation (i) for active TB] should undergo immunization prior to starting anti-TNF treatment. Hepatitis B vaccines are inactivated vaccines and therefore do not contain live organisms and cannot cause hepatitis B in an immunosuppressed individual. There are limited data with regard to response to hepatitis B immunization in patients with rheumatic disease receiving biologic therapy. There is circumstantial evidence indicating that TNF blockade may directly modulate humoral responses [190], with one study suggesting that TNF blockade with ETN decreases responses to the hepatitis B vaccine; patients with RA who were treated with MTX had very good response rates, whereas those treated with an MTX–ETN combination or ETN alone had poor response rates [191]. Therefore, though it is safe to give hepatitis B vaccine to a patient on anti-TNF treatment, if possible, the first hepatitis B vaccine should be given prior to commencing anti-TNF therapy.

Due to the risk of poor response, it is important that immunization against hepatitis B does not encourage relaxation of other measures to prevent exposure to the virus, such as condom use and needle exchange [192].

(ii) Patients >50 years should undergo vaccination against herpes zoster (HZ) assuming there are no contraindications (e.g. treatment within the past 3 months with >40 mg prednisolone per day for >1 week, >20 mg prednisolone per day for >14 days, MTX >25 mg/week, AZA >3.0 mg/kg/day). This should be administered preferably >14 days before starting biologic therapy (grade 2C, SOA 97%).

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The risk and severity of shingles (HZ infection) is considerably higher among immunosuppressed individuals, with evidence suggesting that people with rheumatic diseases have around double the incidence of shingles of the general population [193, 194]. A 2014 meta-analysis including ACR, EULAR and BSR registry data found that the pooled risk ratio for HZ in patients with IA on anti-TNF agents was 1.61 (95% CI: 1.16, 2.23). The proportions of severe HZ ranged from 2.0 to 5.5% with csDMARDS, compared with 4.9–20.9% with TNF-blockers [195].

According to Public Health England recommendations, eligible individuals anticipating immunosuppressive therapy should ideally be assessed for vaccine eligibility before starting treatment that may contra-indicate future vaccination [196]. Eligible individuals who have not received Zostavax should receive a single dose of vaccine at the earliest opportunity and at least 14 days before starting immunosuppressive therapy.

HZ vaccine is now recommended in the UK for all individuals aged 70–79 and a national vaccination programme is underway. Zostavax reduces the risk of shingles by ~50% in immunocompetent adults aged ⩾60 years [197]. Efficacy of the vaccine appears to wane within the years after vaccination, with studies suggesting efficacy of 39.6% for prevention of HZ and 60.1% for prevention of postherpetic neuralgia 4–7 years post-vaccination [198]. It is licensed for the use in individuals aged ⩾50 years, and therefore could not be recommended for patients younger than this [199].

Vaccination has been shown to be associated with reduced incidence of HZ in a study of over 460 000 patients aged ⩾60 years with autoimmune diseases [200]. As HZ vaccine is a live attenuated vaccine, it carries a small risk of infection, particularly in immunosuppressed individuals. However, in this study, among 633 patients with recent or current exposure to biologics at the time of vaccination, no case of HZ or varicella occurred. These data were, however, extracted from administrative claims from hospitals and cases of HZ and varicella were not confirmed with medical records review. Encouragingly, in two further studies, no increased incidence of HZ or varicella zoster was shown following vaccination in individuals with autoimmune disease receiving a variety of biologic therapies [201]. Nonetheless, Public Health England currently recommends that HZ vaccine should not be given to individuals already on biologic therapy or who, in the past three months have received >40 mg prednisolone per day for >1 week, >20 mg prednisolone per day for >14 days, non-biological oral immune modulating drugs (e.g. MTX >25 mg/week, AZA >3.0 mg/kg/day) [196, 202].

(iii) Patients who do not have a positive history of varicella zoster (chickenpox) infection should have a varicella zoster virus antibody test. If this is negative, and there are no contraindications (as listed in (ii)) varicella zoster vaccination should be offered prior to biologic commencement (grade 2C, SOA 98%).

Varicella zoster virus, which causes chickenpox, is more common and serious in immunosuppressed individuals, as they are at risk of severe and potentially fatal disseminated varicella infections [203, 204]. It is the most frequent viral opportunistic infection (OI) seen in patients on MTX or anti-TNF agents [23].

The varicella vaccine is a live attenuated vaccine, and the two-dose vaccination schedule provides around 75% protection in adolescents and adults—mild breakthrough infections can occur in around 10% of adults [205]. For this reason it is not recommended for those already on immunosuppressive medication, such as AZA (>3.0 mg/kg/day), ciclosporin, MTX (>25 mg/week), CYC, LEF or equivalent 40 mg prednisolone/day); this group will cover a significant proportion of patients due to start anti-TNF therapy.

In individuals due to start biologic therapy who are not in the above category, varicella zoster vaccination is recommended, in addition to vaccination of healthy susceptible close household contacts of immunocompromised patients (e.g. children of a patient due to start biologic therapy who have not had varicella zoster). Patients without a definite history of varicella zoster virus infection should undergo a varicella virus antibody test. If negative, and there is no contraindication, they should be offered vaccination on the two-dose schedule. Personal recall of varicella infection has been shown to be a good predictor of serological immunity [206, 207].

For patients receiving biologic therapy

Monitoring on treatment

(i) All patients should be reviewed for drug safety in a specialist department at least every 6 months. High risk patients (e.g. those at high risk of TB) should be reviewed every 3 months (grade 2C, SOA 94%).

There is no evidence on the optimal monitoring requirements for patients receiving biologics. However, in view of the aforementioned potential risks associated with these treatments, and the NICE requirements to ensure a satisfactory clinical response to treatment, we suggest that patients are reviewed at least every 6 months by a rheumatology specialist. Higher risk patients may require more frequent review, as supported by NICE guidance. The 2011 NICE guideline cg117 [76] and the 2005 BTS guideline [208] recommend that high-risk TB patients should be monitored every 3 months (with a CXR and sputum cultures, if respiratory symptoms develop).

(ii) Patients prescribed a biologic (other than TCZ) without concomitant csDMARD (or with csDMARDs that do not require blood test monitoring), should have monitoring blood tests (FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 3–6 months (grade 2C, SOA 97%).

Anti-TNF biologics

Haematological abnormalities have been reported in patients treated with anti-TNF agents but in many cases

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there have been other co-prescribed medications that may have been responsible for these changes. One case series reported neutropaenia ($<2.0 \times 10^9$/l) in 14.3% of 133 RA patients on anti-TNF therapy [209]. A history of previous neutropaenia on csDMARD therapy and a low baseline neutrophil count were shown to be predictors of neutropaenia. Two other studies have reported rates of anti-TNF-induced neutropaenia of 8 and 14% [210, 211]. The majority of reported cases of anti-TNF-induced neutropaenia were mild, did not result in any significant clinical complications and did not require modification in anti-TNF therapy. Reports of anti-TNF-associated pancytopenia and aplastic anaemia are rare but in some cases have been fatal [212].

More recently, a US cohort of 1322 patients receiving anti-TNF therapy had no increase in prevalence of anaemia, leucopenia or thrombocytopenia [213]. Other studies have shown resolution of anaemia of inflammation following treatment with anti-TNF agents. Niccoli *et al*. [214] monitored the FBC of 106 patients with AS over a 6-month period and found Hb, MCV, iron, ferritin, CRP and ESR improved, reaching statistical significance. However, this study is confounded by the simultaneous stopping of NSAIDs on commencement of anti-TNF, perhaps leading to a reduction in insidious GI bleeding.

Liver function test derangement has also, albeit rarely, been associated with anti-TNF therapy. In an observational study of 6861 RA patients, over 6.5 years of follow-up, elevations in AST and ALT were found in 6.67% of patients [215]; however, only 0.77% had levels more than twice the upper limit of normal. IFX (as opposed to ADA or ETN) was associated with the highest frequency of elevations.

Anti-TNF therapy is not known to affect renal function [216]; however, IA is associated with chronic kidney disease [217]. Hence in individuals already undergoing blood monitoring, an assessment of renal function may be useful to detect any deterioration in renal function and enable early investigation and treatment that may prevent further decline.

Thus, in light of reports of pancytopenia and liver function test elevation with anti-TNF therapy, it is recommended that patients undergo blood monitoring on a regular basis (every 3–6 months).

Non-anti-TNF biologics

Late-onset neutropaenia is a recognized side effect of RTX therapy and, although it usually follows a benign course and is infrequent, can present with infection [214, 215]. A UK study of 108 patients receiving RTX for RA between October 2007 and July 2011 identified five patients (4.6%) who developed late-onset neutropaenia (LON; neutrophil count $\leqslant 1.5 \times 10^9$ after a median of 151 days [70–181, 215]; two patients developed pneumonia. A similar rate of 6% (eight patients) was observed in a Norwegian single-centre case review analysis of 133 RA patients, and was more common in those with low IgM and IgG levels [12]. Fifty per cent of patients with LON had infection at the onset of neutropaenia; six patients were rechallenged with RTX without recurrence of LON. In this study it took a median of 6.5 days for recovery of LON.

(iii) Patients receiving csDMARD may require more regular laboratory monitoring (as per BSR/BHPR non-biologic DMARD guidelines, 2017) (grade 2B, SOA 96%).

Patients receiving biologic therapy alongside a csDMARD may require blood test monitoring more frequently than every 3 months, depending on which csDMARD they are receiving. Minimal monitoring requirements for the different csDMARDs and the blood results that require action are given in the 2017 BSR/BHBR non-biologics DMARD guidelines [5]. The blood results that require action are the same as those defined in the BSR 2017 csDMARD guideline [5].

(iv) Patients receiving RTX should have serum immunoglobulins (especially IgG and IgM) checked prior to each cycle of RTX. Clinicians and patients should be aware that the risk of infection increases as serum IgG levels fall below normal. Lower dose RTX may be considered in this situation (grade 2A, SOA 99%).

Lower levels of IgG have been associated with an increased risk of infection in individuals receiving RTX [13]. Van Vollenhoven *et al*. [13] monitored Ig levels every 8–16 weeks in patients with RA receiving RTX and found that following RTX therapy $\leqslant 3.9\%$ had low IgA or total Ig levels at any time, while 14.8 and 37.9% had below normal IgG and IgM levels, respectively, any time. Over the first 5 years of treatment the proportion of patients with IgM but not IgG or IgA below the lower limit of normal continued to increase. Serious infection rates in those patients who developed low IgG levels were higher than the serious infection rates in patients who never developed low IgG; however, this study was limited by low numbers in the low IgG subgroup (143 patients).

Although there is no evidence to suggest an absolute total Ig, IgM or IgG threshold where RTX should not be given, clinicians and patients should be aware that the risk of serious infection increases as serum IgG level falls. Lower dose RTX (such as 2×500 mg infusions) may be considered in this situation [13, 218].

(v) Patients receiving i.v. or s.c. TCZ, with or without MTX, should have laboratory monitoring every 4 weeks for neutrophils and ALT/AST (grade 2B). Blood tests should ideally be in the week before i.v. TCZ, and in the 3 days before every fourth s.c. injection. Any decision to halt treatment should be made in accordance with the guidance in the TCZ SPC (grade 2C, SOA 96%).

TCZ has been found to cause a reduction in absolute neutrophil count (ANC) in a number of studies [219–221]. This is thought to be due to peripheral margination of neutrophils, but is not associated with an increased frequency of infection. Nishimoto *et al.* [220] found that 6% of patients on TCZ experienced neutropaenia grade 3 or 4, with a further 15% having grade 1 or 2. Interestingly, these events were not associated with infection. Nakamura *et al*. [219] found ANC to drop in the first 24 h after i.v. TCZ administration, but the ANC recovered by the next

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infusion 4 weeks later. Maini *et al*. [221] found ANC to reach a nadir at 2 weeks post-infusion, with recovery occurring within the following 2 weeks.

More recently, a double blind, double dummy RCT [222] compared patients receiving TCZ *vs* MTX *vs* TCZ + MTX. No significant difference was seen between the groups in terms of infection or drop in ANC. A 97-week open label extension of a 24-week double blind study comparing i.v. and s.c. formulations of TCZ has shown that even at 97 weeks, a small number of patients still develop new grade 3 or 4 neutropaenia, with numbers similar in both i.v. and s.c. groups (0.81 and 0.76%, respectively) [223].

Rises in transaminases (ALT and AST) have been found with TCZ in a number of studies. Various studies have noted raised transaminases that spontaneously resolved without the need for TCZ dose change [224–228]. Dougados *et al*. [229], and others, found that 41–51% of patients on TCZ in combination with a conventional DMARD will have spontaneously resolving episodes of raised ALT up to three times the upper limit of normal [224, 225, 228, 229]. In a retrospective cohort study looking back over 45 months, Machado-Alba *et al*. [230] found 5/51 (9.8%) patients on TCZ developed a rise in ALT up to three times the upper limit of normal.

The TCZ SPC has detailed guidance concerning when to stop or change therapy in the context of blood test abnormalities and should be referred to (http://www.medicines.org.uk/emc/medicine/22311/-SPC/RoActemra).

(vi) Patients receiving TCZ should have their serum lipids checked at 3 months, and treated appropriately if abnormal; they may be checked again thereafter at physician's discretion (grade 2A, SOA 99%).

TCZ has been noted to cause an initial rise in serum lipids [187, 221, 231], but long-term extension studies have shown them to broadly stabilize within 3 months [232]. A *post hoc* analysis by Gabay *et al*. [233] of 324 patients in the ADACTA trial up to 24 weeks showed that compared with ADA, TCZ was associated with a slightly raised LDL cholesterol level, but the overall lipid profiles were similar. An increase in cardiac events has not been found, perhaps with the deleterious effect of higher lipids being offset by better control of inflammatory disease. Further work is required in this area.

Co-morbidity management on treatment

(i) Patients with significant co-morbidities who are also receiving biologic therapies, should have close involvement with specialists in that field (grade 1C, SOA 99%).

Infection

In general:

(i) All biologics should be discontinued in the presence of serious infection, but can be recommenced once the infection has resolved (grade 1A, SOA 99%).

Anti-TNF biologics

No studies to date have assessed outcomes in patients with IA receiving anti-TNF therapy who did not stop treatment in the presence of severe infection; however, there are data, primarily from case reports, suggesting that infections may become more severe if patients continue with anti-TNF therapy [234]. Patients should be made aware of the increased risk of infection, and should be advised to stop therapy until the infection has resolved.

Non-anti-TNF biologics

As no studies have investigated the outcome in patients continuing with these drugs in the presence of active infection, caution is advised and it is suggested that non-anti-TNF biologics should also be stopped until infection has cleared. Further data in this area are required.

Mycobacterium tuberculosis

(i) Patients commenced on biologics should be closely monitored for TB while on treatment and for at least 6 months after stopping treatment (grade 2C, SOA 98%).

This recommendation is largely based on expert opinion from NICE [76] and the BTS guidelines [208]. Any patient who develops symptoms consistent with TB, even if their pre-biologic TB screening was negative, should be investigated for active TB, initially with a chest X-ray and sputum examination.

Up to a 19% risk of TB reactivation has been reported; however, this varies according to the local rates of a positive TST/IGRA and the local incidence of TB. Most cases of reactivation have occurred during the first year of anti-TNF treatment after completion of chemoprophylaxis [235].

(ii) Patients on biologics who develop symptoms suggestive of TB should receive full anti-TB treatment but may continue with their biologic if clinically indicated after risk/benefit analysis (grade 2C, SOA 96%).

Patients who develop active TB while on biologic treatment should receive full anti-TB chemotherapy [236]. In these circumstances, treatment can be continued if clinically indicated because the patient would otherwise be prevented from receiving the continued clinical benefit to their underlying disease and may have a flare up or major clinical deterioration.

While there is limited evidence in this area, it is reported that HIV positive individuals with reduced CD4 counts and clinical TB, who are even more immunosuppressed than those on anti-TNF treatment, respond equally well to TB treatment as those who are HIV negative [237].

Opportunistic infection

(i) Health-care professionals should have a high index of suspicion for atypical/OIs, especially if current or recent steroid use. Biologic therapy should be

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promptly stopped in suspected cases. Patients should have rapid access to specialist health care for consideration of early treatment (grade 1B, SOA 99%).

Anti-TNF biologics

There have been a few observational cohort studies investigating the association between OIs and anti-TNF use. The largest of these studies, the US Safety Assessment of Biologic Therapy project, found a higher incidence of non-viral OIs compared with patients initiating non-biologic DMARDS [238]. Within the cohort of 33 324 new anti-TNF users over a 9 year period, 80 non-viral OIs were identified with pneumocystosis being the most common, accounting for 20% of OI cases ($n = 16$); histoplasmosis ($n = 9$) and cryptococcus ($n = 3$) were the next most frequently observed fungal OI. Nocardiosis ($n = 12$) had the highest incidence for opportunistic bacterial infection ($n = 12$), followed by salmonellosis [8] and listeriosis ($n = 4$). The overall crude rate of non-viral OI in the TNF group was 2.7 *vs* 1.7 per 1000 person-years in those receiving only csDMARD (adjusted HR = 1.6, 95% CI: 1, 2.6).

Data collected from the US CORONNA registry found that anti-TNF drugs were an independent predictor of OI (bacterial and viral) [23]. One hundred and sixty-four OIs were observed in the TNF-treated group, with an IRR of 1.18 (95% CI: 1.08, 1.32) compared with MTX alone. The combination of MTX and anti-TNF did not appear to further increase the risk of OI above that of anti-TNF alone. In both studies, baseline steroid use was an independent risk factor for OI; however, to date there is insufficient evidence to support the use of primary prophylaxis in this group.

Non-anti-TNF biologics

The risk of non-TB atypical OIs does not seem to be increased with RTX, TCZ, ABA or TCZ compared with other biologics, but long-term data are lacking [59].

Vallabhaneni *et al*. [239] looked at 4000 patients who had received TCZ, and 11 of these (0.28%) developed invasive fungal infections, which is non-inferior to other biologics. There are no observational data regarding the long-term risk of UST and atypical OI.

(ii) In patients exposed to primary varicella through a close household contact [and without a positive history of varicella zoster (chickenpox) infection or vaccination], post-exposure prophylaxis with varicella zoster immune globulin should be considered if the risks from infection are perceived to be significant. Shingles should be treated conventionally (grade 2C, SOA 94%).

Anti-TNF biologics

Several studies have found a significant association between anti-TNF therapy and risk of HZ. The most recent data comes from the Australian ARAD database of 2157 RA patients [42]. RA patients receiving IFX, ETN or ADA had a 37% higher risk of shingles (adjusted hazard ratio (aHR) 1.37, 95% CI: 1, 2.92) compared with csDMARD users. Data from BSRBR-RA showed that patients receiving first generation anti-TNF were found to have an up to 80% higher risk of shingles (aHR = 1.8, 95% CI: 1.2, 2.8; crude incidence of 1.6/100 person-years) [240]. This study, along with data from the RABBIT, BIOBADASER and CORRONA registries, was included in a 2014 meta-analysis, which found a pooled risk ratio for HZ with TNF inhibitors of 1.61 (95% CI: 1.16, 2.23) [195].

Relatively fewer studies have focused on varicella zoster (chickenpox) risk and anti-TNF therapy. Higher rates of hospitalized chickenpox and shingles compared with the general population have been observed in a study combining the BIOBADASER registry with the Spanish national hospital discharge database [241]. The IR for hospitalized shingles and chickenpox in patients receiving anti-TNF therapy was 44 and 26 per 100 000 person-years, compared with an expected IR of 3.4 and 1.9 per 100 000 person-years, respectively, in the general population.

There remains little evidence on the effectiveness of varicella zoster immune globulin (VZIG) in preventing infection in immunosuppressed patients. A study of 81 immunosuppressed children who received VZIG following household exposure to varicella, found a moderate response to VZIG, although 49 children still developed varicella infection, including some who had serological evidence of past exposure [242]. Until more data are available, we feel that it is appropriate to recommend that VZIG is considered as a post-exposure prophylaxis for patients receiving biologic therapies who are exposed to varicella infection in whom the risks of infection are perceived to be high. VZIG is an intramuscular injection, and should be given as soon as possible—not later than 10 days after exposure; a second dose should be given if further exposure occurs >3 weeks after the first dose.

Non-anti-TNF biologics

There have been reports of higher than expected episodes of HZ in patients receiving RTX and ABA from cohort studies [35, 243]. Data are lacking on the risk of TCZ and UST and HZ. Until more data are available, we suggest that the recommendations for anti-TNF therapies be applied to all biologics.

(iii) Clinicians should be vigilant for progressive multifocal leukoencephalopathy (PML), which has been primarily associated with RTX but has also been reported with anti-TNF therapy. Treatment should be stopped if PML develops. Rechallenge is not recommended (grade 1C, SOA 99%).

PML has been reported in a few more patients than was reported on the previous guideline and to date there have been 11 cases in patients with RA [244]. The majority of case have been in association with RTX use, but rarely cases have been reported with other agents [245]. Considering how many more patients have been treated with RTX since the last guideline, this should be

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reassuring of the lack a major signal, but vigilance should still be maintained.

The prognosis for PML is poor, with a high level of mortality at 1 year. Although there is no treatment for PML, stopping biologic therapy may slow progression. There are no data regarding PML receiving biologic therapies for non-RA IA. No cases of PML have been reported with TCZ, ABA or UST.

Hepatitis B and C infection

(i) Close monitoring of serum amino-transaminases and HBV DNA load is recommended in patients with occult or overt HBV infection treated with biologic therapy (grade 1C SOA 99%).

Patients should be followed carefully by means of ALT and HBV DNA testing and treated with anti-viral therapy upon confirmation of HBV reactivation before ALT elevation. The frequency of monitoring can range from 1 to 3 months depending on the type of immunosuppressive therapy and comorbidities [93].

(ii) Close monitoring of serum amino-transaminases and HCV RNA during therapy should be considered in patients with HCV treated with a biologic (grade 1C, SOA 99%).

Studies to date continue to show that biologic (especially anti-TNF) therapies do not have a detrimental effect on HCV infection [99, 101], but it would be prudent to work closely with a hepatologist and arrange monitoring.

(iii) Patients with serological evidence of occult HBV infection may require concomitant anti-viral treatment if detrimental changes in monitoring tests develop (grade 1B, SOA 99%).

Patients with previous occult HBV infection treated with biologic therapy who reactivate their HBV have generally good outcomes even if anti-viral treatment was required [90, 92, 246]. In these studies anti-viral treatment was generally given if HBV DNA level was $>10^5$ IU/ml, although we recommend that thresholds of treatment should be decided working with a hepatologist given that European Association for the Study of the Liver guidelines recommend treatment based on a combination of raised ALT, HBV DNA level >2000 IU/ml and severity of liver disease [93].

HIV

(i) Patients with HIV receiving anti-TNF therapy require close monitoring of viral load and CD4 count. Treatment changes should be made in light of results, with guidance from an HIV specialist (grade 2C, SOA 99%).

Refer to the earlier section on HIV.

Malignancy

(i) Patients should be encouraged to comply with national cancer screening programmes (grade 1C, SOA 99%).

(ii) Patients should be investigated for potential malignancy if clinically suspected and biologics should be stopped if non-BCC malignancy is confirmed (grade 1C, SOA 97%).

There is an absence of evidence regarding the cessation of biologic therapy in the presence of proven malignancy; certainly no studies to date have investigated whether continuing or stopping biologic therapy in this situation has any effect on prognosis. Until any further evidence is available, it is suggested that all biologic therapies should be stopped if malignancy (excluding skin BCC) is confirmed, and any ongoing future treatment discussed with oncology specialists on a case by case basis.

(iii) Biologic therapies may be continued in patients who develop a BCC that is fully excised, after careful discussion with the patient and a risk–benefit analysis (grade 2C, SOA 97%).

There have been no studies to date assessing the outcome of biologic-treated patients who undergo complete excision of a NMSC and continue with biologic therapy. As described earlier, there is evidence to suggest that anti-TNF agents increase the risk of a future NMSC in individuals who have a past history of them [140], but conflicting results have also been reported in other studies [140]. Due to the low inherent risk of metastasis following the complete excision of a BCC, we suggest that in this situation biologic therapies may be continued after careful discussion with the patient and possible input from a dermatology specialist.

Cardiac problems

(i) If patients develop worsening cardiac failure while on anti-TNF, consideration should be given to stopping therapy if no other explanation for worsening cardiac failure is found following input from a cardiologist (grade 2C, SOA 99%).

Although recent studies have reassuringly not found a significant effect of TNF inhibitors on cardiac failure [153, 154], early clinical trials did report a detrimental association [150–152]. There are numerous causes of cardiac failure including ischaemic heart disease, hypertension and valvular heart disease, all of which are more common than drug-induced causes. With this in mind, we suggest that consideration is given to stopping anti-TNF agents in individuals with worsening cardiac failure if this cannot be attributed to other pathologies after specialist input from a cardiologist.

Respiratory disease

(i) Patients with ILD receiving biologics should be regularly reviewed by a respiratory physician with a specialist interest in ILD, and ideally in a combined rheumatology/respiratory clinic. Pulmonary function tests (PFTs) should be performed as clinically indicated, usually every 4–6 months (grade 2C, SOA 99%).

Most ILDs share a restrictive pattern, with reductions in lung volumes and a reduced diffusing capacity for carbon

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monoxide (DLCO). Low baseline forced vital capacity (FVC) and DLCO (e.g. FVC <60% and DLCO <40% of predicted values) are independent predictors of early death in patients with IPF. Serial PFTs add information on disease trajectory. Importantly, a short-term (6–12 month) decline in FVC of ⩾10%, or a decline in DLCO of ⩾15%, is associated with increased mortality in IPF [247]. In one systematic review, where ILD occurs subsequent to introduction of anti-TNF, ∼80% of cases were found in the first 20 weeks with a mean of 26 weeks [167].

Although there are no data to suggest the optimal frequency of pulmonary monitoring, we suggest that routine PFT monitoring should be performed as clinically indicated, usually every 4–6 months.

(i) Consideration, in consultation with a respiratory physician with a specialist interest in ILD, should be given to stopping biologic therapy in patients with worsening or new features of ILD. RTX or ABA may be considered in patients with worsening or new ILD (grade 2C, SOA 90%).

Anti-TNF biologics

Patients demonstrating worsening respiratory symptoms or lung function should have the input of a respiratory physician with a specialist interest in ILD to consider the possible causes of the decline as the differential includes causes potentially related to biologic therapy such as infection, congestive heart failure, progression of RA-ILD, drug-induced pneumonitis or other causes not related to biologic therapy such as COPD or pulmonary emboli.

Although it is difficult to establish causation of worsening or new features of ILD to anti-TNF, and in fact an observational study by Herrinton *et al*. [162] found that anti-TNF therapy was not associated with a diagnosis of ILD in RA patients over a mean follow-up of 3 years, we would still recommend consideration of discontinuation of anti-TNF in these circumstances until data from further, larger studies is available.

Non-anti-TNF biologics

Although it is difficult to establish causation of worsening or new features of ILD to any of the non-anti-TNF biologics, a decision to discontinue therapy should be taken in conjunction with respiratory specialist colleagues with the understanding that based on current levels of evidence, ILD is unlikely to be caused or exacerbated by RTX, ABA or TCZ. There are no data available regarding UST in this context.

Uveitis

(i) If patients develop uveitis while on a biologic a trial of an alternative biologic could be considered, bearing in mind the latest reported relative risks (grade 1C, SOA 99%).
(ii) Consider switching patients with uveitis currently taking ETN to INF or ADA (grade 2C, SOA 98%).

Anti-TNF biologics

Refer to the earlier section on uveitis.

Non-anti-TNF biologics

There has been one case report of a patient with RA treated with TCZ who developed acute anterior uveitis 5 weeks after stopping TCZ [248]. Causality is difficult to establish here and indeed TCZ has been used with moderate success in patients with uveitis [173]. There are no data concerning RTX, ABA or UST and the development of uveitis.

Demyelinating disease

(i) Anti-TNF should be withdrawn if demyelination occurs. Rechallenge with anti-TNF therapy is not recommended (grade 2B, SOA 99%).

Any suspected cases of demyelination should be investigated and reported appropriately and referred urgently to a neurologist. The rationale behind this statement is covered in the earlier section on demyelinating disease.

Sixteen cases of Guillain–Barré syndrome were identified from the FDA database following anti-TNF therapy [249]. Among the 13 patients for whom follow-up data were available, one patient experienced no resolution, nine patients had partial resolution and three patients had complete resolution of Guillain–Barré syndrome following therapy.

There are some reports of successful rechallenge with anti-TNF without recurrence of neurological symptoms, but there are also reports of worsening symptoms or recurrence on rechallenge.

Diverticular disease

(i) TCZ should be withdrawn if bowel perforation occurs; reintroduction of TCZ in such patients is not recommended (grade 2C, SOA 99%).

Refer to the earlier section on diverticular disease.

CTD

(i) If a lupus-like syndrome or other significant autoimmune disease develops while on anti-TNF therapy, treatment should be discontinued and appropriate interventions should be initiated. In such instances, a non-anti-TNF biologic should be considered. Rechallenging with an alternative anti-TNF agent should only be undertaken with caution (grade 1C, SOA 99%).

Anti-TNF biologics

There continue to be further case reports of lupus-like syndromes, vasculitis and other autoimmune conditions developing after the commencement of anti-TNF therapy that improve on cessation of the anti-TNF, but often requiring alternative immunosuppression in more severe cases. Full-blown anti-TNF induced lupus or vasculitis remains rare.

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In a study by Takase *et al*. [250], 18% of patients had ANA seroconversion (83 of 454) when monitoring ANA results while on an anti-TNF, with seroconversion after a median period of 11 months. Only three of these patients were classifiable as lupus, however. BSRBR-RA reported on 11 394 anti-TNF patients followed for a total of 26 927 person-years [251]. Forty anti-TNF-treated patients developed a new lupus event, compared with only one of the DMARD-treated patients (adjusted IRR = 3.17, 95% CI: 0.38, 26.26). The most common lupus symptom was skin rash; LN or neuropsychiatric symptoms were not reported.

Ramos-Casals *et al*. [252] identified 379 patients affected by an autoimmune condition induced by an anti-TNF through a Medline search up to May 2008. SLE/lupus-like disease was found in 105 patients. SLE criteria met were most commonly ANA positive, anti-dsDNA positive, malar rash then arthritis, with <10% having renal or CNS involvement. Treatment was anti-TNF withdrawal in 93% of cases. Thirty-six patients needed steroid or immunosuppression. Mean follow-up was 10 months, and all improved.

A retrospective review of Mayo clinic records 1998–2011 [253] looked at the clinical features, histopathological features and outcomes where diagnosis of vasculitis induced by anti-TNF had been made. Cutaneous small vessel vasculitis was the most common but systemic involvement including peripheral nerve and renal vasculitis was frequently observed; mean duration of anti-TNF prior to development of vasculitis was 34.5 months (2–72 month range). Follow-up after vasculitis was a mean 27.1 months (1–108). No recurrence was seen in these patients on stopping anti-TNF and there was a mean time of 6.9 months to resolution of vasculitis after stopping anti-TNF with all receiving adjuvant treatment. No patients were rechallenged with an anti-TNF agent.

In conclusion there are reports to suggest a small number of patients are at risk of developing a lupus or vasculitis problem when treated with anti-TNF but it is rare to have major organ involvement and symptoms usually resolve on stopping anti-TNF. Although only small numbers of patients have been rechallenged with anti-TNF, when undertaken this led to recurrence in up to 75%, hence the recommendation to use caution if considering rechallenge [252, 254, 255].

Non-anti-TNF biologics

There are no data to suggest an association between any of the non-anti-TNF biologics and induction of autoimmune CTD or vasculitis.

Haematological disorders

(i) Biologic therapies may be continued in patients at increased risk of, or with, venous thromboembolism (VTE) (grade 2C, SOA 99%).

Anti-TNF biologics

Although some studies have reported a potential increased risk of VTE in anti-TNF users [256], a retrospective cohort study using BSRBR-RA data compared the rates of VTE in RA treated with anti-TNF ($n = 11881$) with those treated with csDMARD ($n = 3673$) and found no difference in the rates of VTE between anti-TNF and csDMARDs [257]; the risk was similar across all anti-TNF agents. The study was, however, not powered to detect differences of small magnitude. It should be noted that the observational nature of the BSRBR-RA predisposes to channelling bias (patients with more severe disease are more likely to be enrolled into the anti-TNF cohort). Therefore, continuation of biologic therapies in patients at increased risk can be recommended, as, in addition, higher disease activity may predispose to a prothrombotic state [258]. Risk would also be increased if active disease caused immobility.

Non-anti-TNF biologics

There are no data to suggest that any of the non-anti-TNF biologics increase the risk of VTE.

Psoriasis

(i) If psoriasis develops in patients treated with anti-TNF, conventional psoriasis treatment should be started and consideration should be given to stopping anti-TNF if the skin lesions persist despite specialist dermatology input or are severe (grade 2B, SOA 99%).

Anti-TNF biologics

Several studies have suggested that anti-TNF agents may paradoxically increase an individual's risk of developing psoriasis, despite these agents being licensed and approved by NICE for the treatment of psoriasis.

BSRBR-RA compared 9826 RA patients receiving anti-TNF agents (either IFX, ETN or ABA) against 2880 csDMARD patients [259]. Over 520 person-years of follow-up, 25 cases of new onset psoriasis were observed in those receiving anti-TNF, 52% of which occurred within the first 6 months of therapy, compared with 0 cases in the csDMARD group; this equated to a crude IR of 1.04 (95% CI: 0.67, 1.54) *vs* 0 (95% CI: 0.71) per 1000 person-years. In this cohort, the highest rates of psoriasis were found with ADA compared with ETN and INF.

A higher incidence of psoriasis has also been found in the BIOBADASER cohort [260]. Out of 4437 patients receiving first-generation anti-TNF agents, 32 cases of psoriasis were observed, with an IR of 2.31 (95% CI: 1.69, 3.15). In this cohort, the highest event rate was noted for INF, and the lowest for ETN.

The majority of patients who develop psoriasis while receiving anti-TNF agents do not stop therapy, and are able to manage the condition with add-on therapy [258, 260, 261]. In the BSRBR-RA cohort, only 4 of the 13 patients who developed psoriasis in the first 6 months of anti-TNF therapy stopped treatment due to psoriasis; all reported improvement in psoriasis after stopping therapy [258]. Similarly, a retrospective review of the Mayo clinic experience identified 56 RA patients who developed psoriasis while receiving anti-TNF treatment [260]. Of these, 62% continued with therapy and were treated

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successfully with add-on medication, although higher rates of complete skin remission were observed in those that stopped treatment. The most common forms of psoriasis that occurred in this cohort were plaque psoriasis and palmopustular psoriasis. A literature review by Collamer and Battafarano [262] found that around 50% of patients who switch to an alternative ant-TNF agent due to psoriasis will not experience a recurrence of their lesions.

Non-anti-TNF biologics

There is no convincing data to suggest an association between any of the non-anti-TNF biologics and the development of psoriasis.

Vaccinations

(i) The Public Health England recommendations on the use of immunizations in patients on immunosuppressive therapy should be adhered to in patients on biologics. Live attenuated vaccines, such as the HZ vaccine, oral polio or rabies vaccine, should be avoided (grade 2C, SOA 99%).

Public Health England recommend that live attenuated vaccines should not be routinely given to individuals who are immunosuppressed (including those receiving biologic therapy). Live attenuated organisms can replicate in an immunosuppressed individual and cause an extensive, serious infection. If the use of live vaccines is necessary, at least 2 weeks, but preferably 4 weeks should be allowed before anti-TNF therapy is commenced.

In terms of travel advice, yellow fever is a live vaccine and must not be given, and therefore patients should be advised not to travel to countries requiring this (e.g. mid-African nations). An exemption statement may be given if a patient has to travel but the patient will be at risk.

Measles, mumps and rubella are live vaccines, so should not be given to a patient on anti-TNF but the vaccine is not contraindicated in household contacts. Exposure to measles should be treated with immunoglobulin regardless of prior immunization [263].

BCG vaccine for TB is contraindicated in patients on anti-TNF treatment as it is also a live vaccine [264].

Polio vaccine is an inactivated vaccine so may be given to immunosuppressed individuals (live polio vaccine was used up until 2004 in the UK) [265].

(ii) Although there may be an attenuated response (particularly if MTX is co-prescribed), patients on biologics should receive influenza and pneumococcal immunizations unless there are contraindications (grade 1C, SOA 99%).

Patients receiving immunosuppressive therapy are advised to have both influenza and pneumococcal immunization. A limited number of studies are available investigating the response to vaccination in rheumatoid patients, with assessments made on RA patients treated with either MTX alone or in combination with anti-TNF.

Influenza immunization

Anti-TNF biologics

There is some evidence that there are differences in response to immunization between each of the first-generation anti-TNF agents. While ADA has been shown not to reduce responsiveness to immunization [266], some studies have suggested that ETN and INF administration is associated with decreased response rates [267, 268]. A study by Elkayam *et al*. [269] showed an adequate response overall to influenza vaccine in patients with RA on INF, but a slightly attenuated response in the group that were vaccinated 3 weeks after receiving INF rather than on the same day. However, numbers were small (38 patients on INF, seven given vaccine 3 weeks after INF) [269]. A review [267] of influenza studies has indicated that this immunization is well tolerated; however, a subset of patients may remain unprotected. Some patients may be concerned that the influenza vaccine may provoke a flare of their RA. However, reassuringly, a recent study published by Milanetti *et al*. [270] noted no increase in flares of RA in patients receiving influenza immunizations, but a slight increase in minor systemic and local side effects such as fever, injection site swelling, headaches and myalgia.

Non-anti-TNF biologics

The efficacy of the influenza vaccine in patients treated with RTX has been examined in several cohort studies. A meta-analysis by Hua *et al*. [271] has shown that some response occurs, but it is attenuated if the patient is on the drug. Response rates may improve if vaccination is given further away from the last RTX infusion; Westra *et al*. [272] found that the IgG response to vaccination was restored in patients who had received RTX 6–10 months prior to vaccination. IgM response, however, did not change.

There is a small amount of evidence regarding the other non-anti-TNF biologics and their effect on response to influenza vaccine. A small Brazilian study of 11 RA patients receiving ABA found a reduced immune response to the influenza vaccine [273]. There are no data concerning TCZ and UST and the influenza vaccination.

Although there are limited data and the suggestion that response to vaccination may be attenuated, because non-anti-TNF biologics are immunosuppressive medications, it is recommended that all patients receiving biologic therapies continue to have a yearly influenza vaccination.

Pneumococcal immunization

Anti-TNF biologics

While MTX is associated with lower response rates to pneumococcal vaccines in most studies [274–277], some studies have suggested that ETN or INF in combination with MTX are not associated with a poor response [266, 274–276]. The reasons for these differences are unclear, but the theory that certain anti-TNF agents can lead to enhanced immune responses was put forward from one study [274], where patients with MTX had lowered responsiveness, but this does not explain why those

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with the combination of INF or ETN with MTX had even better response rates than the healthy controls.

In the case of ADA, ADA alone has not been shown to affect the antibody titre response to pneumococcal immunization, but the combination of MTX and ADA was shown to be associated with decreased response rates when compared with MTX alone [266].

More recent evidence from a Swedish case–control study [278] in a group of 505 patients with RA or SpA showed adequate response rates to pneumococcal vaccine. Better antibody response ratios were seen in patients on anti-TNF monotherapy, compared with those treated with MTX or MTX plus anti-TNF. Ongoing MTX was predictive of reduced response.

Overall, pneumococcal vaccine is recommended in patients receiving anti-TNF therapy, but clinicians should be aware that the response to vaccination may be attenuated if anti-TNF and MTX are used in combination.

Non-anti-TNF biologics

A small study by Crnkic Kapetanovic *et al*. [279] found that among 88 patients with RA, the antibody response to the pneumococcal vaccine was reduced most notably for RTX, but also with ABA; TCZ, on the other hand, was associated with a sufficient antibody response. There are no data regarding treatment with UST and response to the pneumococcal vaccine.

(iii) In patients who are currently receiving biologics, human papillomavirus vaccine for cervical cancer risk in young women is recommended if they have already received part of the vaccination schedule, as per national guidelines (grade 2C, SOA 99%).

There is a national human papillomavirus (HPV) childhood vaccination programme in place in the UK, introduced in 2008 for secondary-school-age girls of 12–13 years, although girls may receive their HPV vaccination programme up to their 18th birthday. There are no data for the two-dose schedule for immunocompromised patients, and therefore the three-dose schedule should be given if a girl has already started or is due to start anti-TNF therapy. National advice states that re-immunization should be considered after treatment has finished or recovery occurred, and specialist advice may be required [280]. Kumar *et al*. [281] described reduced immunogenicity in organ transplant recipients.

Although most at-risk individuals will have received papillomavirus vaccine in childhood, there may be scenarios where young adults receiving biologics over the age of 18 have not received vaccination. We suggest that in these circumstances, vaccination should be offered, even though the individual is outside of the national vaccination programme age window.

Peri-operative care

(i) The potential benefit of preventing post-operative infections by stopping biologics (different surgical procedures pose different risks of infection and wound healing) should be balanced against the risk of a peri-operative flare in disease activity (grade 2B, SOA 97%).

(ii) For most biologics (exceptions: RTX and TCZ), consideration should be given to planning surgery when at least one dosing interval has elapsed for that specific drug; for higher risk procedures consider stopping 3–5 half-lives (if this is longer than one dosing interval) before surgery (grade 2B, SOA 97%).

(iii) Biologics may be recommenced after surgery when there is good wound healing (typically around 14 days), all sutures and staples are out, and there is no evidence of infection (grade 1B, SOA 99%).

(iv) For patients receiving RTX, treatment should ideally be stopped 3–6 months prior to elective surgery (grade 2B, SOA 94%).

(v) For patients receiving TCZ, i.v. TCZ should be stopped at least 4 weeks before surgery; s.c. TCZ should be stopped at least 2 weeks before surgery (grade 1C, SOA 96%).

Anti-TNF biologics

Current literature provides conflicting data with regard to the risk of infection peri-operatively in association with anti-TNF therapy. A Dutch retrospective study [282] of 1219 surgical procedures in RA patients found that peri-operative continuation of anti-TNF therapy did not seem to be an important risk factor for surgical site infection. This is supported by evidence from several smaller studies [283, 284]. Larger studies from Canada [285], Japan [286] and Germany [287] showed no significant differences in surgical site infection rates in patients on anti-TNF therapy compared with csDMARDS; however, biologic therapy was withheld peri-operatively in >80% of cases. Another Japanese study of orthopaedic surgery found no statistically significant increase in the incidence of delayed wound healing or superficial infection with anti-TNF agents [288]. There was no correlation between peri-operative disease activity, dose of ETN (25 *vs* 50 mg) or preoperative waiting period off biologics (<14 or >14 days) and likelihood of adverse events.

Conversely, other studies have reported an increased risk of peri-operative infection rates with continued use of anti-TNF agents [289]. One report showed that the continuation of anti-TNF therapy was associated with an increased risk of peri-operative infections (OR = 4.4, 95% CI: 1.10, 18.41) in a series of 91 RA patients undergoing orthopaedic procedures [290]. Data from the BSRBR-RA [291] showed that the risk of serious post-operative infection was nearly 2-fold higher in patients who received anti-TNF therapy in the 28 days prior to surgery than in those who were not exposed.

Two further Japanese studies have supported these findings, with suggestion of even greater increased risk of peri-operative infection on anti-TNF. A retrospective cohort study of 420 women with RA, Momohara *et al*. [292] found that anti-TNF agents (INF, ETN, ADA) increased the risk of surgical site infection 9-fold. A

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Table 7 Dosing intervals, recommendations for timing of surgery and half-lives of biologic therapies

Drug	Dosing interval	Period in which surgery should be scheduled (relative to last biologic dose administered)	One half-life, days	Five half-lives, days
Adalimumab	Every 2 weeks	Week 3	14	70
Abatacept i.v./s.c.	Monthly (i.v.) weekly (s.c.)	Week 5 Week 2	14	70
Certolizumab	Every 2 weeks Every 4 weeks	Week 3 Week 5	14	70
Etanercept	Weekly or twice weekly	Week 2	3	15
Golimumab	Every 4 weeks	Week 5	14	70
Infliximab	Every 4, 6 or 8 weeks	Week 5, 7 or 9	9	45
Rituximab	Two doses 2 weeks apart, no more frequent than every 6 months	Months 4–7	18	90
Tocilizumab i.v.	Every 4 weeks	Week 5		
4mg/kg			11	55
8mg/kg			13	65
Tocilizumab s.c.	Every week	Week 3	13	65
Ustekinumab	Every 12 weeks	Week 13	21	105

higher risk still was identified in a smaller case–control study of 64 patients [293]; INF and ETN were associated with an OR of 21.8 for surgical site infection (95% CI: 1.231, 386.1; $P = 0.036$). ETN was withheld for 2–4 weeks prior to the operation and INF for 4 weeks prior to the surgery. Critics have suggested that the cases of infection were overstated, however, as infections were counted 'when surgeons diagnosed or suspected a surgical infection, and antibiotics were given prophylactically'. Surgeons were not blind regarding which patients had been exposed to anti-TNF therapy, and so could have had a higher index of suspicion for infection in patients on anti-TNF and hence be more likely to prescribe antibiotics [294]. Blinded, prospective studies are therefore needed before firm conclusions can be drawn about the infection risk associated with anti-TNF agents.

In 2008, Pappas and Giles [295] identified six major studies investigating the peri-operative infection risk of anti-TNF therapy associated specifically with orthopaedic surgery. All studies assessed involved retrospective outcome data and the source populations differed greatly between studies making direct comparison difficult. Of the six published major studies, only one study [290] identified an increased risk associated with peri-operative anti-TNF exposure, but the authors recommended that anti-TNF therapy should be stopped for a duration of three to five times their half-lives pre-operatively and restarted once the wound healing is deemed satisfactory (10–14 days). The half-lives of biologic therapies are shown in Table 7. This may be manageable for those biologic agents with reasonably short half-lives, but with agents such as ADA and ABA, where five times the half-life equates to >2 months, cessation for this prolonged period of time is likely to lead to potentially significant (and possibly irreversible) declines in the disease control and major flare, often requiring steroid therapy (and the associated risks, which may be higher than biologic therapy).

Pragmatically we suggest that surgery should be arranged for the week after the next scheduled dose of anti-TNF, and longer still (preferably five half-lives) if the surgery is deemed to be of especially high infection risk by the surgical team. With INF, five half-lives of the drug (45 days) may actually be shorter than the dosing interval, for example, patients receiving INF every 8 weeks. In this situation, ensuring that one dosing interval has elapsed before surgery should be sufficient even with procedures deemed to have a higher risk of infection. The idea behind this dosing principle is that the nadir of the drug's effect would be at the end of its dosing interval. This is in line with advice from a recently published systematic review by the ACR and American Association of Hip and Knee Surgeons [296].

Non-anti-TNF biologics

There is a paucity of data specific to non-anti-TNF biologics and peri-operative care.

A retrospective study using the French AIR registry [297] identified 133 patients who had received RTX prior to a surgical procedure. Eight (6.7%) of the patients experienced a post-operative complication, including eight site infections and one deaths due to septic shock. Post-operative complications were higher in orthopaedic than abdominal surgery; however, only a significant association was seen with spinal surgery ($P = 0.048$). All patients had stopped RTX prior to surgery a mean of 6.4 months beforehand (interquartile range 4.3–8.7 months). There was no difference in event rates according to length of time off therapy prior to surgery. Unfortunately the study could not differentiate between acute and elective procedures, but 68% of procedures were orthopaedic. The number of complications was small and whether the time from infusion to complication of surgery is a major factor was difficult to interpret.

TCZ is a very potent suppressor of acute phase response. A retrospective study looking at 161 patients on

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TCZ for RA undergoing orthopaedic surgery found 20 patients with wound healing delay, and three post-operative infections, two of which were superficial [292]. This study had no comparator, so conclusions are difficult to draw. Another study comparing patients undergoing surgery on TCZ and csDMARDS found those on TCZ did not mount as high a fever or as significant a rise in CRP as the csDMARD group. Following an infusion of i.v. TCZ, CRP and other markers of acute phase response reach a nadir between 1 and 3 weeks and then gradually return to normal. Although data are lacking, monitoring for post-operative infections in the first 4 weeks following a TCZ infusion is likely to be significantly hampered by a blunted acute phase response. Patients having i.v. or s.c. TCZ might need close monitoring in the post-operative period as the conventional indicators of sepsis (fever and acute phase response) might not be reliable. There are no data regarding ABA and UST in the peri-operative period.

Until further evidence is available, and considering the balance between the potential risk of peri-operative complications *vs* the potential for disease flare if patients are without therapy for a prolonged period of time, we suggest that RTX is stopped at least 3–6 months prior to elective surgery; i.v. TCZ should be stopped at least 4 weeks prior to and s.c. TCZ at least 2 weeks prior to surgery. For all other non-anti-TNF biologics we suggest that surgery should be arranged for the week after the next scheduled dose of anti-TNF, and longer still (preferably five half-lives) if the surgery is deemed to be of especially high infection risk by the surgical team.

Applicability and utility

Clinician responsibility

These guidelines represent a framework upon which clinical practice should be based. However, as with any guideline, individual patient circumstances can have important influences on clinical decision-making, and clinicians should continue to work alongside patients to make shared decisions about care. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence.

Potential organizational barriers to the guideline

Biological therapy initiation should only take place under the supervision of an expert in the management of rheumatic disease (i.e. a consultant rheumatologist)—a recommendation supported across the NICE guidelines across the rheumatic disease areas.

An important consideration regarding biologic therapy monitoring is the impact of frequent blood monitoring on health care services. Effective biologic therapy monitoring requires systems in place not only to ensure patients have regular blood tests, but also that the results of tests are reviewed and acted upon appropriately within a timely manner.

The guideline makes three specific recommendations that will increase monitoring burden, as described below.

All patients to be reviewed for drug safety in a specialist rheumatology department at least every 6 months. High risk patients (e.g. those at high risk of TB) should be reviewed every 3 months.

Patients prescribed a biologic (other than TCZ) without concomitant csDMARD or with csDMARDs that do not require blood monitoring should have monitoring blood tests (FBC, renal and liver function) every 3–6 months.

Patients prescribed i.v. or s.c. TCZ, with our without MTX, should have monitoring blood tests (FBC, liver function) every 4 weeks.

Audit tool

A model audit tool template is available for biologic therapy imitation and monitoring. The audit tool can be accessed via the BSR website.

Overall summary and conclusions

Biologic therapies represent a major advance in the treatment of IA, and appropriately their use continues to increase. Information on the longer term safety of these drugs continues to be collected both at a local level and through national registries across the world. Data remain scarce for the second-generation TNF inhibitors (CZB and GOL) and some of the newer non-anti-TNF biologic therapies (such as TCZ, ABA and UST). Similarly, there is a paucity of longer term observational safety data for any of the biosimilar therapies recently licensed and in increasing use worldwide. As questions in many commonly encountered clinical scenarios remain unanswered, it is essential that data on the safety of these products continue to be captured and reported, to inform further updates of this guideline.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: C.R.H. has been sponsored to attend meetings by AbbVie, Pfizer, Bristol-Myers Squibb and UCB and has received honoraria for speaking and attended advisory boards with AbbVie, Bristol-Myers Squibb, Pfizer, UCB, Janssen and Novartis. R.S. has received sponsorship to attend the national BSR conference from Pfizer and has received honoraria to speak at regional educational meetings by AbbVie and Eli Lilly. M.B. has been sponsored to attend regional, national and international meetings by UCB Celltech, Roche/Chugai, Pfizer, AbbVie, Merck, Mennarini, Janssen, Bristol-Myers Squibb, Novartis and Eli Lilly and received honoraria for speaking and attended advisory boards with Bristol-Myers Squibb, UCB Celltech, Roche/Chugai, Pfizer, AbbVie, Merck, Mennarini, Sanofi aventis, Eli Lilly, Janssen and Novartis. A.M. has received honoraria for sponsored presentations from MSD, Bristol-Myers Squibb and Roche and received an honorarium from Pfizer for professional services. C.H. has received sponsorship to attend a national meeting by Pfizer. E.C. has received sponsorship to attend meetings by Pfizer and UCB and received honoraria for speaking for Eli Lilly.

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C.C. has received sponsorship to attend a national meeting by Pfizer. A.L. has received sponsorship to attend meetings and courses by AbbVie, Roche and UCB and has received honoraria for speaking by Roche/Chugai. J.T. has received honoraria from Hospira. S.B. has received sponsorship to attend a national meeting by Pfizer. All other authors have declared no conflicts of interest.

Acknowledgements

The GWG acknowledges the contribution from the following advisors: HIV section: Professor Karen Walker-Bone, MRC Lifecourse Epidemiology Unit, University of Southampton; TB section: Dr Ben Marshall, Consultant Respiratory Physician and Honorary Senior Lecturer, University Hospital Southampton. We would also like to acknowledge the contribution of the previous anti-TNF safety GWG.

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Gout

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RHEUMATOLOGY

Rheumatology 2017;56:e1-e20
doi:10.1093/rheumatology/kex156

Guidelines

The British Society for Rheumatology Guideline for the Management of Gout

Michelle Hui[1], Alison Carr[2], Stewart Cameron[3], Graham Davenport[4], Michael Doherty[5], Harry Forrester[4], Wendy Jenkins[5], Kelsey M. Jordan[6], Christian D. Mallen[4], Thomas M. McDonald[7], George Nuki[8], Anthony Pywell[5], Weiya Zhang[5] and Edward Roddy[4,9] for the British Society for Rheumatology Standards, Audit and Guidelines Working Group

Scope and purpose

Background to the disease

Gout is the most common cause of inflammatory arthritis worldwide. In UK general practice, the overall prevalence has increased from 1.4% in 1999 to 2.49% in 2012 [1], despite the availability of effective and potentially curative urate-lowering drugs for >50 years and evidence-based British and European management guidelines for nearly a decade [2, 3].

Clinical manifestations of gout resulting from monosodium urate crystal deposition include tophi, chronic arthritis, urolithiasis and renal disease as well as recurrent acute arthritis, bursitis and cellulitis. Gouty arthritis and tophi are associated with chronic disability, impairment of health-related quality of life [4–7], increased use of healthcare resources and reduced productivity [8]. Gout is also frequently associated with co-morbidities such as obesity, dyslipidaemia, diabetes mellitus, chronic renal insufficiency, hypertension, cardiovascular disease, hypothyroidism, anaemia, psoriasis, chronic pulmonary diseases, depression and OA [1] as well as with an increase in all-cause mortality (adjusted hazard ratio 1.13, 95% CI: 1.08, 1.18) and urogenital malignancy [1, 9].

Sustained hyperuricaemia is the single most important risk factor for the development of gout. Hyperuricaemia occurs secondarily to reduced fractional clearance of uric acid in > 90% of patients with gout [10]. Age, male gender, menopausal status in females, impairment of

NICE has accredited the process used by the BSR to produce its guidance for the management of gout. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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Submitted 18 November 2016; revised version accepted 8 March 2017.

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renal function, hypertension and the co-morbidities that comprise the metabolic syndrome are all risk factors for incident gout associated with decreased excretion of uric acid, as are the use of diuretic and many anti-hypertensive drugs, ciclosporin, low-dose aspirin, alcohol consumption and lead exposure. Tophi and chronic arthritis [11], alcohol consumption [12] and recent use of diuretic drugs [13] are important risk factors for recurring flares.

Genome-wide association studies have identified a number of genes coding for urate anion transporters expressed in the proximal renal tubular epithelium, but these account for <5% of the variation in serum urate [14]. Serum urate levels are influenced by dietary intake and synthesis as well as by renal excretion. Diets high in red meat or seafood, and increased consumption of beer, spirits and fructose- or sugar-sweetened soft drinks are established risk factors for developing gout [15–17]. Single gene disorders associated with urate overproduction, hyperuricaemia and accelerated purine synthesis *de novo* (such as glycogen storage diseases and Lesch–Nyhan syndrome) are very rare causes of primary gout. Diseases (such as lympho- and myeloproliferative disorders and severe exfoliative psoriasis) and drugs (such as cytotoxics, vitamin B12 and ethanol) associated with increased cellular turnover and destruction can lead to secondary hyperuricaemia and gout [18].

The identification of monosodium urate crystals in joint and tissue samples remains the gold standard for the diagnosis of gout. Although identification of urate deposits by dual-energy CT [19] and US [20] are being used increasingly as an aid to the diagnosis of gout in research and hospital practice, joint aspiration or imaging to confirm crystal presence is rarely undertaken in primary care settings where the majority of patients with gout are managed. For diagnosis in clinical practice, clinical scores, without imaging or synovial fluid analysis, have been proposed [21] that include consideration of the patient's history and co-morbidities.

Need for revised management guideline

The British Society for Rheumatology/British Health Professionals in Rheumatology (BSR/BHPR) guideline for the management of gout was published in 2007 [2]. There are four broad reasons why a revised and updated guideline is now required. First, new pharmaceutical treatment options have become available and the evidence base for the efficacy and safety of available drugs has expanded. Second, the incidence, prevalence and severity of gout have increased [1] despite the availability of safe, effective and potentially curative therapy. Third, research studies and audits have consistently shown that fewer than 50% of patients with gout seen in general practice receive urate-lowering therapy (ULT) [22–25] and that many patients with gout being treated with ULT in both primary [1, 26] and secondary care [27, 28] do not achieve reductions of serum uric acid (sUA) levels to the target level recommended in the BSR/BHPR (300 μmol/l) or EULAR (360 μmol/l) guidelines. Finally, as evidence has accumulated that the provision of information to patients with gout is suboptimal [29] and qualitative studies have begun to define a range of patient and provider barriers to effective care [30–32], preliminary data are emerging that demonstrate that these barriers can be overcome, and outcomes improved, with better provision of information and a package of care based on guideline recommendations [33].

Other guidelines available

Recently published guidelines include the 2012 ACR Guidelines for the Management of Gout [34, 35] and the 2013 evidence-based recommendations for the diagnosis and management of gout by a multinational panel of rheumatologists participating in the 3e initiative [36]. Other national and regional guidelines include the US Agency for Healthcare Research and Quality's 2014 guidelines for Diagnosis of Gout and Management of Gout [37, 38], and the Australian and New Zealand [39] and Portuguese [40] recommendations for the diagnosis and management of gout that arose from the 3e initiative [36]. Updated EULAR recommendations for the management of gout were published in 2016.

Objective

This guideline aims to offer revised and updated, concise, patient-focused, evidence-based, expert recommendations for the management of gout in the UK.

Target audience

The guideline has been developed to provide assistance to doctors and allied health professionals who treat and manage patients with gout in primary care and hospital practice. The guideline should also provide a helpful resource for patients and those responsible for commissioning care for patients with gout in the National Health Service (NHS).

Areas that the guideline does not cover

Evidence-based recommendations for the diagnosis and investigation of gout are not included in this guideline. Some recommendations for the diagnosis of gout are addressed in the recent 3e recommendations for the diagnosis and management of gout [36] and EULAR recommendations for the diagnosis of gout [3] are in the process of being updated [41].

Stakeholder involvement

The guideline has been developed by a Multidisciplinary Working Group of rheumatologists (M.H., M.D., K.J., G.N., E.R.), general practitioners (G.D., C.M.), secondary care physicians with specialist experience in general internal medicine, clinical pharmacology (T.M.), and nephrology (S.C.), allied health professionals (A.C., W.J.), lay patients (H.F., A.P.), and an epidemiologist with expertise in evidence-based medicine (W.Z.), on behalf of the BSR/BHPR Standards, Audit and Guidelines Working Group. The draft guideline was presented and discussed in open session by a multidisciplinary audience at the annual scientific meetings of the BSR in 2014 and 2016. The consensus recommendations were developed without any input

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from, or consultation with, any pharmaceutical company and potential conflicts of interest of all members of the working group have been fully declared. This guideline has been reviewed and endorsed by the Royal College of General Practitioners.

Rigour of development

Scope of the guideline and strategy for guideline development

The scope of the revised guideline and the key clinical management questions that needed to be addressed were agreed by consensus at an initial face-to-face meeting of the guideline working group after detailed review of the published guideline and results of a systematic literature review. Seventeen clinical management questions (Table 1) were subsequently subjected to additional focused systematic literature searches after transposition into 20 questions in Population, Comparator, Outcome, Time format [42].

Systematic literature search

Systematic literature searches were undertaken by M.H. using MEDLINE 1946 to present, EMBASE 1974 to present, PubMed from inception to present, the Cochrane Controlled Trials Register from inception to present and the ISI Web of Science and AMED databases 1985 to present. An initial literature search in March/April 2012 was updated in June 2015 (see Supplementary table S1, available at *Rheumatology online*, for search strategy).

Inclusion criteria

Articles included were systematic reviews, randomized controlled trials (RCTs), uncontrolled trials, observational studies including cohort, case–control and cross-sectional studies, or those where economic evaluation was made.

Exclusion criteria

Editorials, commentaries, conference abstracts and non-evidence-based narrative/personal reviews were excluded. Studies of hyperuricaemia were included only if they related to the management of gout.

Delphi exercise to generate consensus recommendations

Concise consensus recommendations for the management of gout were developed. Members of the guideline working group were asked to generate a comprehensive list of propositions for the management of gout based on available research evidence and their own clinical expertise after reviewing the published recommendations and the results of the systematic literature reviews. Following elimination of closely similar and overlapping recommendations, a preliminary list of 51 proposed recommendations included 13 for the management of acute gout, 15 relating to education, diet and lifestyle modification, and 23 for the management of recurrent, inter-critical and chronic gout. Consensus for 30 revised draft recommendations was reached after three rounds of a Delphi exercise conducted by email in which propositions with >60% of votes were accepted, those with <20% rejected and those attracting between 20 and 60% of votes reconsidered after amalgamations and minor rewording. The draft recommendations were presented for discussion and feedback at the annual scientific meeting of the BSR in 2014. Final consensus on the most appropriate wording for 21 recommendations was agreed at a second face-to-face meeting of the guideline working group after further minor amalgamations and discussion

Table 1 Principal clinical questions considered

1. In patients with acute gout, does the use of ice packs reduce pain?
2. In patients with acute gout, what medication should be used to manage acute attacks?
3. For patients on diuretic therapy presenting with acute gout, should diuretic therapy be discontinued?
4. What are the potential patient and healthcare professional barriers to management of patients with gout?
5. Is patient education effective for patients with gout and, if so, in what format?
6. Is dietary advice effective in the management of patients with gout?
7. In patients with gout and renal failure, should the dose of allopurinol be adjusted?
8. Should patients with gout be screened for co-morbidities?
9. In patients with hyperuricaemia or gout, when should urate-lowering therapy be commenced?
10. In patients with gout, should allopurinol be used as first-line urate-lowering therapy?
11. In patients with gout, should febuxostat be used as an alternative urate-lowering therapy to allopurinol and, if so, in what situations?
12. In patients with gout, should other medications such as benzbromarone, sulfinpyrazone and probenecid be used?
13. In patients initiating urate-lowering therapy, for how long should prophylactic colchicine be continued?
14. In patients initiating urate-lowering therapy, should canakinumab and rilonacept be used to prevent gout attacks?
15. In patients with hyperuricaemia, gout and hypertension, should an angiotensin II blocker rather than an angiotensin-converting enzyme blocker be used?
16. In patients with gout and hyperlipidaemia, should fenofibrate be used as an adjunctive urate-lowering agent?
17. In patients with debilitating chronic tophaceous gout refractory to oral urate- lowering drugs, or in whom these drugs are contraindicated, should pegloticase be used?

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of the draft recommendations and the feedback from members of the BSR.

Level of evidence

The level of evidence (LoE) in support of each recommendation was determined (1a: meta-analysis of RCTs; 1b: at least one RCT; IIa: at least one well-designed controlled study without randomization; IIb: at least one well-designed quasi-experimental study; III: at least one non-experimental descriptive study, for example, comparative, correlation or case–control study; IV: expert committee reports, opinions and/or experience of respected authorities) [43]. Where a superior LoE was found, for example, a systematic review for a particular intervention, preceding studies regarding that intervention were not further analysed.

Strength of recommendation

The strength of recommendation (SOR) for each treatment recommendation by members of the guideline development group was graded anonymously on a 0–100 mm visual analogue scale by those present at the final face-to-face meeting and by the others via email.

The SOR for each management recommendation was based on the opinions of the guideline working group after considering the research evidence for efficacy, safety and cost-effectiveness of each treatment proposed, and the personal expertise of each member of the group [44]. This included considerations such as the experts' experience and perception of patient tolerance, acceptability and adherence to the treatment in question, as well as their expert knowledge of any logistic issues involved in the administration of the recommended treatment. A simplified algorithm (Fig. 1) illustrates the suggested care pathway.

Recommendations

Recommendations for management of acute attacks

(i) Educate patients to understand that attacks should be treated as soon as an attack occurs and ensure that patients are aware of the importance of continuing any established ULT during an attack. LoE: IV; SOR: 90% (range 81–100%).

Rationale

The SOR for educating patients to understand the importance of treating acute attacks of gout as early as possible is largely based on common sense, patient experience and expert opinion because of the severity of pain experienced by patients with acute gout. Reduction of pain within 24 h following treatment with an NSAID [45] and with colchicine [46] has, however, been demonstrated in two small placebo-controlled RCTs. The recommendation to continue treatment with urate-lowering drugs during acute gout flares is based on a widespread consensus of expert opinion [2, 34, 47], and qualitative studies that suggest that many patients are unaware of the need to do so [30, 31].

(ii) Affected joints should be rested, elevated and exposed in a cool environment. Bed-cages and ice-packs can be effective adjuncts to management. LoE: Ib (ice-packs), IV (other); SOR: 89% (range 54–100%).

Rationale

The recommendation to rest acutely affected joints is based on widespread patient experience and expert opinion. While there is evidence that urate crystal-induced experimental arthritis in dogs is aggravated by movement and ameliorated by rest [48], there have been no RCTs of rest undertaken in patients with gout. The recommendation for using ice is supported by a Cochrane systematic review of a single small RCT (n = 19) in which topical ice was added to prednisolone and colchicine [49]. In this trial, greater pain reduction (−3.3 cm, 95% CI: −5.84 to −0.82 on 10 visual analogue scale) was observed with adjunctive use of ice packs without additional adverse events. Ice packs may be used as safe adjuncts to pharmacological treatment for acute gout, or when drugs are contraindicated because of multiple active co-morbidities.

(iii) An NSAID at maximum dose or colchicine in doses of 500 μg bd-qds is the drug of choice when there are no contraindications. Choice of first-line agent will depend on patient preference, renal function and co-morbidities. Patients on NSAIDs or cyclooxygenase-2 inhibitors (coxibs) should be co-prescribed a gastro-protective agent. LoE: Ia; SOR: 95% (range 80−100%).

Rationale

Khanna *et al.* [50] recently published a systematic review that included 30 papers examining the management of acute gout. Although NSAIDs are used more often than colchicine in general practice [24], evidence that either is consistently more effective is lacking, so that choice should be determined by individual patient's preference as well as by renal function and co-morbidities.

The efficacy of NSAIDs is supported by a single placebo-controlled RCT of tenoxicam 40 mg daily [45]. Most RCTs have been head-to-head comparisons with no single agent having greater efficacy. There is, however, widespread expert consensus that, where there is no contraindication to do so, NSAIDs should be prescribed at high dose when treating patients with acute gout because of the severity of the pain and inflammation [2, 3, 35]. NSAIDs are, however, frequently contraindicated in patients with renal insufficiency, peptic ulceration or a history of previous upper gastrointestinal haemorrhage or perforation. Selective cyclooxygenase-2 inhibitors such as etoricoxib have equal efficacy and better gastrointestinal tolerability than non-selective NSAIDs [51], but there are ongoing uncertainties about their relative cardiovascular and renal toxicity with chronic administration [52].

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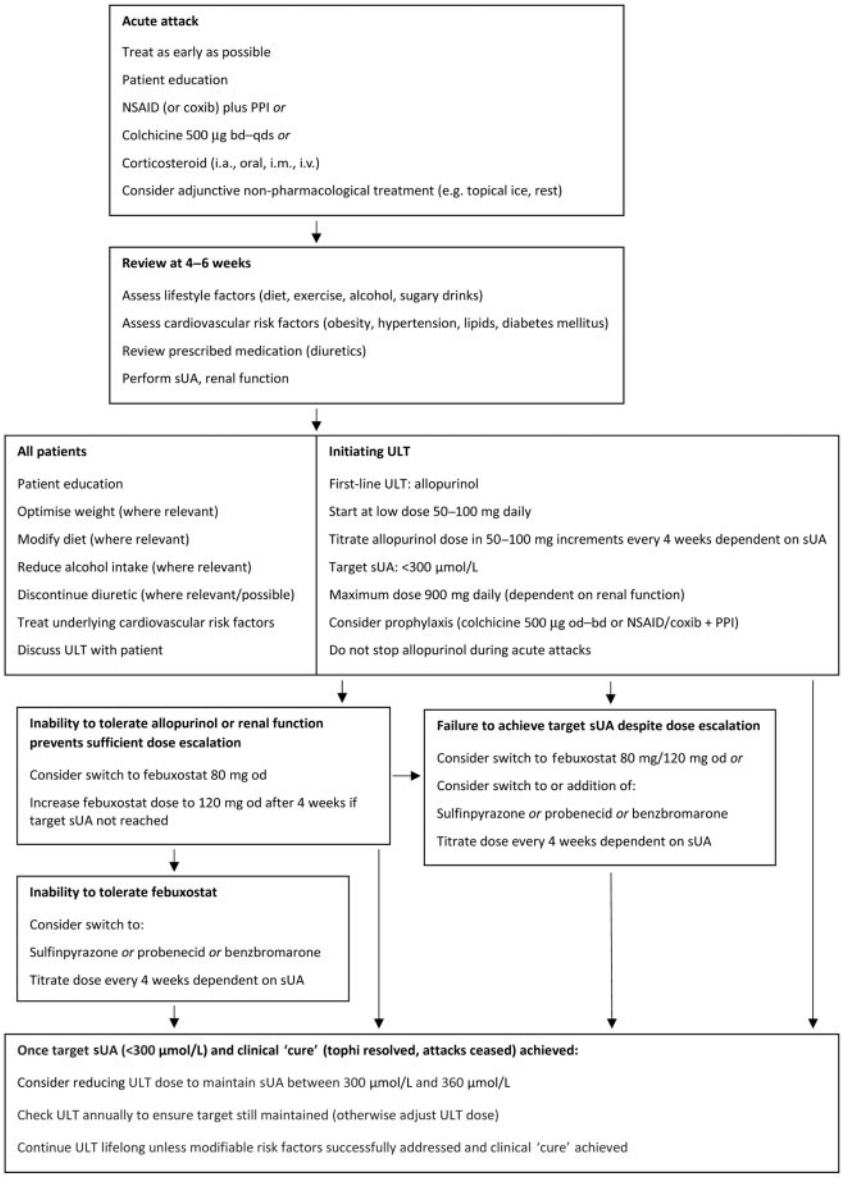
Fig. 1 Algorithm for the management of gout


Acute attack
Treat as early as possible
Patient education
NSAID (or coxib) plus PPI or
Colchicine 500 μg bd–qds or
Corticosteroid (i.a., oral, i.m., i.v.)
Consider adjunctive non-pharmacological treatment (e.g. topical ice, rest)
Review at 4–6 weeks
Assess lifestyle factors (diet, exercise, alcohol, sugary drinks)
Assess cardiovascular risk factors (obesity, hypertension, lipids, diabetes mellitus)
Review prescribed medication (diuretics)
Perform sUA, renal function
All patients
Patient education
Optimise weight (where relevant)
Modify diet (where relevant)
Reduce alcohol intake (where relevant)
Discontinue diuretic (where relevant/possible)
Treat underlying cardiovascular risk factors
Discuss ULT with patient
Initiating ULT
First-line ULT: allopurinol
Start at low dose 50–100 mg daily
Titrate allopurinol dose in 50–100 mg increments every 4 weeks dependent on sUA
Target sUA: <300 μmol/L
Maximum dose 900 mg daily (dependent on renal function)
Consider prophylaxis (colchicine 500 μg od–bd or NSAID/coxib + PPI)
Do not stop allopurinol during acute attacks
Inability to tolerate allopurinol or renal function prevents sufficient dose escalation
Consider switch to febuxostat 80 mg od
Increase febuxostat dose to 120 mg od after 4 weeks if target sUA not reached
Failure to achieve target sUA despite dose escalation
Consider switch to febuxostat 80 mg/120 mg od or
Consider switch to or addition of:
Sulfinpyrazone or probenecid or benzbromarone
Titrate dose every 4 weeks dependent on sUA
Inability to tolerate febuxostat
Consider switch to:
Sulfinpyrazone or probenecid or benzbromarone
Titrate dose every 4 weeks dependent on sUA
Once target sUA (<300 μmol/L) and clinical 'cure' (tophi resolved, attacks ceased) achieved:
Consider reducing ULT dose to maintain sUA between 300 μmol/L and 360 μmol/L
Check ULT annually to ensure target still maintained (otherwise adjust ULT dose)
Continue ULT lifelong unless modifiable risk factors successfully addressed and clinical 'cure' achieved

coxib: cyclooxygenase-2 inhibitor; PPI: proton pump inhibitor; sUA: serum uric acid; ULT: urate-lowering therapy.

Co-prescription of gastro-protection is recommended for patients treated with NSAIDs in accordance with National Institute for Health and Care Excellence (NICE) clinical guidelines [53].

For colchicine, Khanna *et al*. [46, 54] found two placebo-controlled RCTs demonstrating statistical reduction in pain at 24 and 48 h. Terkeltaub's study demonstrated that a low-dose colchicine regimen (1.2 mg followed by 600 μg after 1 h) was equally effective, and was associated with much less nausea, vomiting and diarrhoea, as a high-dose regimen of 4.8 mg over 6 h. A Cochrane review of the same two RCTs [55] also concluded that there was low quality evidence for the efficacy of low-dose colchicine and for no additional efficacy with high doses, which were significantly more likely to be associated with adverse effects (risk ratio (RR) = 3.00, 95% CI: 1.98, 4.54). In the absence of further trial evidence for the efficacy and safety of this proposed regimen, the BSR working group recommends treating acute gout with colchicine in doses of 500 μg bd–qds when there are no contraindications to doing so. The maximum dose of 500 μg qds is, however, often limited by gastrointestinal side effects, most frequently diarrhoea. Colchicine is contraindicated in patients with estimated glomerular filtration rate (eGFR) <10 ml/min/1.73 m^2 and doses should be reduced in patients with eGFR 10–50 ml/min/1.73 m^2 and in the elderly

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[56]. Colchicine should also only be used with caution and at low doses in patients taking drugs that are potent inhibitors of cytochrome P450 3A4 (e.g. cimetidine, clarithromycin, erythromycin, fluoxetine, ketoconazole, protease inhibitors, tolbutamide) or p-glycoprotein (e.g. clarithromycin, ciclosporin, erythromycin) [57]. Caution is also required when using colchicine in patients receiving statins, particularly in those with renal impairment, as there are case reports of myopathy and rhabdomyolysis following combined use of colchicine and statins [58–60].

(iv) Joint aspiration and injection of a corticosteroid are highly effective in acute monoarticular gout and may be the treatment of choice in patients with acute illness and co-morbidity. A short course of oral corticosteroid or a single injection of an intramuscular corticosteroid is an alternative in patients who are unable to tolerate NSAIDs or colchicine and in whom intra-articular injection is not feasible. Such systemic therapy is also appropriate for oligo- or polyarticular attacks of gout. LoE: Ib (oral), III (intraarticular, intramuscular), IV (oligo/polyarticular attacks); SOE: 94% (range 83–100%).

Rationale

A Cochrane review in 2013 [61] found no RCTs of intra-articular steroid use for the management of acute gout. However, small observational studies, expert opinion and clinical experience suggest that intra-articular and intramuscular steroid injections can be very effective treatments for acute gouty arthritis [62–64].

A Cochrane review of systemic corticosteroids [65] for acute gout included one randomized double-blind equivalence trial that showed that 5-day courses of naproxen 500 mg twice daily and prednisolone 35 mg daily had equal efficacy [66].

(v) In patients with acute gout where response to monotherapy is insufficient, combinations of treatment can be used. LoE: IV; SOR: 80% (28–100%).

Rationale

This recommendation is supported only by expert opinion [67]. A survey in 2006 [68] found that the most commonly used combination agents are NSAIDs with either intra-articular corticosteroids, or oral steroids or colchicine.

(vi) IL-1 inhibitors may be considered in patients who have previously not responded adequately to standard treatment of acute gout (although not approved by NICE). LoE: Ib (canakinumab, rilonacept), III (anakinra); SOR: 61% (range 8–100%).

Rationale

Anakinra, canakinumab and rilonacept are three IL-1 inhibitors that have been investigated to some extent for the management of acute gout [69–74]. In an RCT, the mAb anti-human IL-1β antibody canakinumab (150 mg by subcutaneous injection) showed good efficacy in reducing pain and swelling when compared with 40 mg intramuscular triamcinolone acetonide [69, 70]. Canakinumab is licensed for use in Europe by the European Medicines Agency (EMA) but not in the USA by the Food and Drug Administration (FDA) because of uncertainty about its risk/benefit ratio. There are currently no published RCTs for the use of anakinra, an IL-1 receptor antagonist, in patients with gout. However, an open label study using 100 mg s.c. on three consecutive days demonstrated pain relief in patients with gout who could not tolerate or had failed conventional treatment [72] and a retrospective review of its use off-label in 26 patients suggested that it could be an effective and safe alternative treatment for acute gouty arthritis in medically complex hospitalized patients who fail or cannot undergo more conventional therapy [73].

These findings and ongoing uncertainty concerning the efficacy and safety of IL-1 inhibitors are reflected in a recent Cochrane review [74]. None of anakinra, canakinumab and rilonacept is approved by NICE for use in the treatment of acute gout. Prescribers in the UK should be aware of the potential need to obtain approval for an individual funding request before these drugs are used.

Recommendations for modification of lifestyle and risk factors

(i) If diuretic drugs are being used to treat hypertension rather than heart failure, an alternative antihypertensive agent can be considered as long as blood pressure is controlled. LoE: IV; SOR: 91% (range 85–100%).

Rationale

Thiazide and loop diuretics are used for a number of indications including the management of hypertension, heart failure and other causes of fluid overload. Whilst diuretics have been found to be associated with an increased risk of gout with a rate ratio of 11.8 (95% CI: 5.2, 27.0) [75], blood pressure control may require a number of agents and often includes a diuretic [76]. A systematic review published in 2012 [77] attempted to assess the risk, but as the number of studies was small, it concluded that there was insufficient evidence to recommend the discontinuation of diuretics across all indications in patients with gout. A recent population-based case–control study using the General Practice Research Database demonstrated that while the use of thiazide and loop diuretics was associated with the development of incident gout, the use of potassium-sparing diuretics was not [78].

(ii) All patients with gout should be given verbal and written information about the following: the causes and consequences of gout and hyperuricaemia; how to manage acute attacks; lifestyle advice about diet, alcohol consumption and obesity; and the rationale, aims and use of ULT to target urate levels. Management should be individualized and take into account co-morbidities and concurrent medications. Illness perceptions and potential

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barriers to care should be discussed. LoE: IIb; SOR: 96% (range 83–100%).

Rationale

There is growing evidence regarding the importance of education in gout. An observational, proof of concept study [33] has demonstrated how education and individualized lifestyle advice along with ULT can achieve therapeutic targets. In this study of 106 participants, 92% achieved the therapeutic target, adherence at 1 year was excellent, and there were improvements in pain and other patient-centred outcomes.

Qualitative studies [30] suggest that an inadequate understanding of the causes and consequences of gout, belief that it is only a man's disease, and a stereotypical view of gout as being entirely self-inflicted through lifestyle abuse are important barriers to care. This may result in gout sufferers being hesitant in seeking medical advice and adhering to pharmacological treatments that are not well explained. Other studies have shown that such negative views about gout and its treatment are associated with lower adherence to ULT and suboptimal control of disease [32, 79, 80]. Patients who do not, or cannot, adhere to prescribed ULT are more likely to experience more gout attacks more frequently and in more joints. Such factors, as well as co-morbid disease, have been found to be associated with poorer health-related quality of life [6]. While patients are frequently interested in details of the influence of dietary constituents, they commonly also have important concerns relating to drug safety and drug interactions that are seldom adequately discussed [31].

(iii) In overweight patients, dietary modification to achieve a gradual reduction in body weight and subsequent maintenance should be encouraged. Diet and exercise should be discussed with all patients with gout, and a well-balanced diet low in fat and added sugars, and high in vegetables and fibre should be encouraged: sugar-sweetened soft drinks containing fructose should be avoided; excessive intake of alcoholic drinks and high-purine foods should be avoided; inclusion of skimmed milk and/or low fat yoghurt, soy beans and vegetable sources of protein, and cherries in the diet should be encouraged. LoE: I (vitamin C and skimmed milk), III (others); SOR: 92% (range 80–100%).

Rationale

A recent systematic review of predominantly observational studies [81] identified a number of modifiable dietary factors that were associated with gout. Excessive consumption of meat, seafood, alcoholic drinks (especially beer and spirits), sugar-sweetened soft drinks and fructose-containing foods are all significant risk factors for incident gout. Episodic excessive alcohol consumption, regardless of type of alcohol-containing beverage, is also associated with an increased risk of recurrent gout attacks [82]. Low-fat dairy intake, folate intake, coffee consumption and diets high in dietary fibre appear to be associated with a reduced risk of incident gout as well as a reduction in risk of recurrent gout flares in some, but not all, cases [83]. Fruit consumption has been found beneficial and this may be related to consumption of vitamin C (see recommendation VIII for the optimal use of urate-lowering therapies).

The urate-lowering effect of cherry was previously reported in healthy women [84]. A case-crossover study conducted in 633 subjects with gout [85] found that consumption of cherry and cherry extract was associated with a statistically significant 35% lower risk of gout attacks when compared with no cherry intake. When cherry intake was combined with allopurinol use, the risk of gout attacks was 75% lower than during periods without either exposure (odds ratio (OR) = 0.25, 95% CI: 0.15, 0.42).

A Cochrane systematic review of the efficacy and safety of dietary supplements in patients with gout found only two RCTs, one for skimmed milk powder (SMP) enriched with glycomacropeptides (n = 120) and the other for vitamin C (n = 40) [86]. Pain from self-reported flares was marginally less in those receiving enriched, compared with unenriched, SMP (mean difference −1.03, 95% CI: −1.96 to −0.10), but enriched SMP was no better in reducing the mean number of acute attacks or the sUA. Vitamin C (500 mg/day for 8 weeks) reduced the sUA (−0.014 mmol/l) much less than allopurinol (−0.118 mmol/l) in patients with gout, and also less than the mean reduction of 0.02 mmol/l reported in the meta-analysis of 13 RCTs of vitamin C administration in patients with hyperuricaemia who did not have gout [87]. Vitamin C supplementation in this modest dose does not appear to have a clinically significant uricosuric effect in patients with gout [87]. It is certainly insufficient for use as monotherapy and a trial suggested that its efficacy as a urate-lowering agent, even when used as an adjunct to standard ULT with allopurinol, was minimal [88].

(iv) Patients with gout and a history of urolithiasis should be encouraged to drink >2 l of water daily and avoid dehydration. Alkalinization of the urine with potassium citrate (60 mEq/day) should be considered in recurrent stone formers. LoE: IV; SOR: 57% (range 17–100%).

Rationale

While there are no published trials of prevention of urolithiasis in patients with gout and recurrent stone formation, there have been two recent systematic reviews and meta-analyses of RCTs of medical management of recurrent urolithiasis in all adults [89, 90]. There is moderate strength evidence from relatively poor quality RCTs for risk reduction with increased fluid intake (RR = 0.45, 95% CI: 0.24, 0.84) and further reduction of risk with additional therapy with citrates (RR = 0.25, 95% CI: 0.14, 0.44).

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(v) Cardiovascular risk factors and co-morbid conditions such as cigarette smoking, hypertension, diabetes mellitus, dyslipidaemia, obesity and renal disease should be screened for in all patients with gout, reviewed at least annually and managed appropriately. LoE: III; SOR: 90% (range 77–100%).

Rationale

Co-morbidities associated with gout are well recognized [81, 91, 92]. The need to manage these co-morbidities is also recognized but at present no prescriptive guidance exists. An RCT found that allopurinol slows the progression of renal disease in patients with chronic kidney disease (CKD) and hyperuricaemia [93]. The importance of screening for co-morbidities is highlighted by a recent population-based study that has demonstrated gout to be an independent risk factor for mortality from coronary heart disease and renal disease [94].

Recommendations for optimal use of urate-lowering therapies

(i) The option of ULT should be explained to patients when the diagnosis is confirmed and they are being given information about gout. Patients should be fully involved in the decision as to when to commence ULT. The importance of taking ULT regularly and continually to prevent the return of gout attacks should be explained. Patients should be supported during the process of lowering their serum uric acid levels as it can cause an increase in gout flares during this time. LoE: Ib; SOR: 94% (range 82–100%).

Rationale

Reasons for full patient involvement have been discussed earlier in this guideline and are supported by preliminary evidence from a proof of concept study [33]. Poor patient understanding of the need for ULT is not confined to the UK and has been documented in a large population-based observational study in the USA [80], in a survey conducted in South China [95] and in a focus group qualitative study in New Zealand Maoris [96].

(ii) Urate-lowering therapy should be discussed and offered to all patients who have a diagnosis of gout. ULT should particularly be advised in patients with the following: recurring attacks ($\geqslant 2$ attacks in 12 months); tophi; chronic gouty arthritis; joint damage; renal impairment (eGFR < 60 ml/min); a history of urolithiasis; diuretic therapy use; primary gout starting at a young age. LoE: Ia (attacks, tophi, chronic gouty arthritis, joint damage, renal impairment), III (urolithiasis), IV (diuretics, young age). SOR: 95% (range 82–100%).

Rationale

Research evidence supporting the treatment gout with ULT has increased considerably in the last decade. Treatment of patients with recurring attacks, tophi and chronic gouty arthritis is supported by three systematic reviews and meta-analyses [97–99]. However, the recommendation to consider treatment with ULT in all patients with gout is only based on expert opinion and increasing imaging evidence that gout is a chronic crystal deposition disease even at the time of the first attack [100]. For patients known to have other pre-existing risk factors or co-morbidities when presenting with the first episode of gout, such consideration is particularly pertinent. The length of time between the first and subsequent episode of gout can vary considerably between individuals, but typically is < 2 years. Over time, the inter-critical periods shorten and as good practice in patient education, it is worth having the discussion about treatment early in the course of the disease, always bearing in mind that this potentially curable condition can have a significant impact on patient quality of life if left untreated [5, 6]. It is not recommended that asymptomatic hyperuricaemia is treated. However, the wisdom of the recommendation that commencement of ULT should at least be considered after the first attack of gout is supported by observational data from the UK Clinical Practice Research Datalink that showed that less than half the patients with gout eligible for ULT were offered treatment [23].

Earlier recommendations to offer treatment with ULT only to gout patients with recurring acute attacks were supported by a health economic study in a Canadian healthcare setting that showed that only 62% of patients with gout had a second attack within 1 year and that treatment with ULT only became cost-effective (cost saving) in patients suffering more than three attacks per year [101]. This study, however, does not take into account the ongoing silent deposition of crystals and the significant pain experienced by patients with each attack. Clinical experience and epidemiological studies [102, 103] also show that the risk of gout attacks rises sharply when the serum urate is very high (>500 μmol/l). However, the decision as to when to start ULT in any individual will also be influenced by the patient's co-morbidities, any potential contraindications, intolerance or drug interactions, as well as by consideration of the overall balance of risks and benefits and the patient's wishes.

A large population-based study has demonstrated that gout is an independent risk factor for mortality and specifically for death due to coronary heart disease and renal disease [94]. Gout is a risk factor for the development of end-stage renal failure [104] and hyperuricaemia is an independent risk factor for renal impairment [105]. There is now evidence from RCTs that allopurinol slows progression in hyperuricaemic patients with CKD [93, 106] and a recently published systematic review supports the concept that treating gout with ULT improves renal function [55].

Treatment of patients with gout and urolithiasis with ULT is supported by observational studies [107], while the recommendation to consider ULT in patients taking diuretic drugs is supported by three cohort studies and four case–control studies that demonstrated higher risks

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of gouty arthritis in users compared with non-users of diuretics [77].

The recommendation to treat patients with primary gout at an early age with ULT is largely based on expert opinion. A number of rare monogenic disorders associated with inborn errors of purine metabolism [108, 109], glycogen storage diseases [110] or uromodulin mutations associated with decreased fractional urate excretion [111] can result in the development of gout at an early age. A retrospective study of patients seen by rheumatologists in Taiwan suggested that the age at which gout presents was falling [112] and heritability accounts for 35% of gout risk in men and 17% in women in Taiwan [1]. Common dysfunctional variants in the ABC G2 urate transporter may be important causes of early onset gout in Japanese males [113] and in Han Chinese [114] but ~~e~~vidence from twin studies in the USA suggests that while genetic factors have an important influence on serum urate levels and hyperuricaemia, lifestyle and environmental factors are more important risk factors for primary gout, outside the context of the rare single gene disorders [115].

(iii) Commencement of ULT is best delayed until inflammation has settled as ULT is better discussed when the patient is not in pain. LoE: IV; SOR: 94% (range 87–100%).

Rationale

Although a small RCT has shown that commencement of allopurinol during an acute attack was not associated with a significant increase in daily pain, recurrent flares or inflammatory markers [116], the working group thought that postponing detailed discussion of long term ULT until a time when the patient was no longer in pain would allow the information to be better absorbed. However, in patients in whom attacks are so frequent to make this difficult, the findings of this trial support initiation of ULT before inflammation has resolved.

(iv) The initial aim of ULT is to reduce and maintain the sUA at or below a target level of 300 μmol/l to prevent further urate crystal formation and to dissolve away existing crystals. The lower the sUA the greater the velocity of crystal elimination. After some years of successful treatment, when tophi have resolved and the patient remains free of symptoms, the dose of ULT can be adjusted to maintain the sUA at or below a less stringent target of 360 μmol/l to avoid further crystal deposition and the possibility of adverse effects that may be associated with a very low sUA. LoE: III (sUA target <300 μmol/l), IV (subsequent dose adjustment to sUA <360 μmol/l); SOR: 97% (range 90–100%).

Rationale

The target sUA of <300 μmol/l recommended in the previous BSR/BHPR guideline [2] remains the recommended target to prevent crystal formation and recurrent flares [117]. Evidence that greater velocity of crystal elimination is associated with a lower sUA is derived from observational data [118, 119]. The recommendation for ULT dose reduction to the less stringent target of sUA below 360 μmol/l once the patient is stable to avoid further crystal deposition and the possibility of adverse effects that may be associated with a very low sUA is based on expert opinion, a reasoned proposal for such a two-stage approach [119] and caution in the light of studies that have shown a possible association between low sUA levels and progression of neurodegenerative disorders such as Parkinson's disease [120], dementia [121], Huntingdon's disease [122] and amyotrophic lateral sclerosis [123]. One study showed an increased risk of incident Parkinson's disease in men with sUA <300 μmol/l compared with those with sUA 300–500 μmol/l [124].

(v) Allopurinol is the recommended first-line ULT to consider. It should be started at a low dose (50–100 mg daily) and the dose then increased in 100 mg increments approximately every 4 weeks until the sUA target has been achieved (maximum dose 900 mg). In patients with renal impairment, smaller increments (50 mg) should be used and the maximum dose will be lower, but target urate levels should be the same. LoE: Ib (dose escalation), III (dose adjustment for renal function). SOR: 97% (range 88–100%).

Rationale

Research evidence for the efficacy and safety of allopurinol has been studied in a recent systematic review [125]. Eleven trials involving a total of 4531 patients compared allopurinol in various doses with placebo (two trials); febuxostat (four trials); benzbromarone (two trials); colchicine (one trial); probenecid (one trial); continuous *vs* intermittent allopurinol (one trial); and different doses of allopurinol (one trial). In double blind RCTs, allopurinol given in a fixed dose of 300 mg daily was more effective than placebo [126] but less effective than febuxostat 80 mg or 120 mg daily [126, 127]. However, these trials, and observational studies of gout being treated in UK general practice [33], have shown that many patients do not achieve reductions of sUA to target levels recommended by the BSR (300 μmol/l) [2] or EULAR (360 μmol/l) [3] when treated with allopurinol in doses of 300 mg or less daily. Recent data from the Nottingham proof of concept study [33] and from the Febuxostat versus Allopurinol Streamlined Trial (FAST) [128] have confirmed that gradual up-titration of allopurinol is effective in lowering sUA to target levels and generally well tolerated. The median dose of allopurinol found to be required to achieve the less stringent therapeutic sUA target of ⩽360 μmol/l in >90% of the Nottingham patients was 400 mg/day. While we await direct comparison between allopurinol and febuxostat (and other ULTs) using recommended, best practice, up-titration regimens rather than fixed doses, allopurinol should remain the first option. The recommendation that allopurinol should be the first-line ULT

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to consider is further supported by health economic studies [129, 130].

Although well tolerated by the majority of patients, allopurinol is rarely (~0.1–0.4%) associated with potentially life-threatening severe, cutaneous adverse reactions (SCAR) including toxic epidermal necrolysis, hypersensitivity drug reactions with rash, eosinophilia and systemic symptoms (DRESS) or Stevens–Johnson syndrome with vasculitis, liver and renal toxicity [131]. Allopurinol should not be used in people carrying the variant allele HLA-B*5801 [132] as the risk of SCAR during treatment with allopurinol is greatly increased (OR = 73) [133]. Screening patients of Korean, Han Chinese and Thai descent for HLA-B*5801 before considering ULT with allopurinol has been recommended [35] because of the high frequency (6–12%) of this allele in these ethnic groups compared with <2% in Caucasian populations.

Based on reports of a relationship between the use of full dose allopurinol and the development of allopurinol hypersensitivity in patients with renal impairment, previous recommendations were to dose allopurinol according to creatinine clearance (CrCl) [134]. Unfortunately subsequent observational studies showed that dose adjustment according to CrCl seldom resulted in adequate reduction of sUA in patients with gout and renal insufficiency [135], and a case–control study showed no evidence of a reduction in frequency of allopurinol hypersensitivity in patients dosed according to CrCl [136]. More recently, studies by Stamp *et al.* [137] have suggested that lowering the starting dose of allopurinol appropriate to the level of renal function (Table 2) reduces the risk of allopurinol hypersensitivity, and that subsequent gradual increase in the dose above the dose based on CrCl resulted in reduction of sUA to target levels in most patients without any increase in toxicity [138].

(vi) Febuxostat can be used as an alternative second-line xanthine oxidase inhibitor for patients in whom allopurinol is not tolerated or whose renal impairment prevents allopurinol dose escalation sufficient to achieve the therapeutic target. Start with a dose of 80 mg daily and, if necessary, increase after 4 weeks to 120 mg daily, to achieve therapeutic target. LoE: Ia; SOR: 90% (range 63–100%).

Table 2 Starting regime of allopurinol according to glomerular filtration rate

Estimated GFR ml/min/1.73 m^2	Allopurinol starting dose
<5	50 mg/week
5–15	50 mg twice weekly
16–30	50 mg every 2 days
31–45	50 mg/day
46–60	50 mg and 100 mg on alternate days
61–90	100 mg/day
91–130	150 mg/day
>130	200 mg/day

From Stamp LK *et al.* Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. *Arthritis Rheumatol* 2012;64:2529–36. Copyright © 2012 by John Wiley & Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc. GFR: glomerular filtration rate.

Rationale

Systematic reviews and meta-analyses [97, 99] of RCTs [126, 127, 139], among other RCTs, have demonstrated the efficacy of febuxostat in reducing sUA levels, and reducing the risk of gout flares. When compared with a fixed dose of 300 mg of allopurinol, febuxostat (80 mg and 120 mg/day) was more effective in reducing the sUA to <360 mmol/l (RR = 1.56; 95% CI: 1.22, 2.00) but not the risk of gout flares (RR = 1.16; 95% CI: 1.03, 1.30) [97]. There was heterogeneity in the dosages of febuxostat and allopurinol used, the length of time patients had had gout, the length of follow-up, and whether prophylaxis was used.

Febuxostat is generally well tolerated and can be used in doses of 80 mg or 120 mg daily in elderly patients [140] and others with mild to moderate renal impairment (GFR >30 ml/min/1.73 m^2). There are currently insufficient data available on its use in patients with more severe CKD. Severe cutaneous hypersensitivity reactions to febuxostat [141–144] are very unusual but the risk of SCAR or DRESS with febuxostat in patients with previous allopurinol hypersensitivity has still to be established. Treatment with febuxostat in patients with ischaemic heart disease or congestive cardiac failure is currently not recommended [143, 144] but large scale RCTs are currently in progress in Europe [128] and North America [145] to establish and compare the cardiovascular safety of febuxostat and allopurinol in patients with gout, high cardiovascular risk and co-morbidities.

Health economic studies have shown that febuxostat is cost-effective as a second-line ULT [129, 130]. In the UK, NICE have recommended the use of febuxostat only when allopurinol is contraindicated or not tolerated [144] while the Scottish Medicines Consortium (SMC) accepts febuxostat as a suitable second-line ULT when treatment with allopurinol is inadequate, not tolerated, or contraindicated [146].

(vii) Uricosuric agents can be used in patients who are resistant to, or intolerant of, xanthine oxidase inhibitors. The preferred drugs are sulfinpyrazone (200–800 mg/day) or probenecid (500–2000 mg/day) in patients with normal or mildly impaired renal function, or benzbromarone (50–200 mg/day) in patients with mild to moderate renal insufficiency. LoE: Ia; SOR: 92% (range 82–100%).

Rationale

Uricosuric drugs were the first agents to be used for ULT >60 years ago [147]. Their efficacy and safety for ULT is supported by a recent systematic review and meta-

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analysis [148] of two RCTs comparing benzbromarone with allopurinol, two RCTs comparing benzbromarone with probenecid and one non-randomized case–control trial comparing probenecid with allopurinol, and a cohort study examining probenecid [149], but there have been no placebo-controlled RCTs of the three drugs that are currently approved for use as ULT in patients with gout in Europe (sulfinpyrazone 200–800 mg od, probenecid 250–500 mg qds, benzbromarone 50–200 mg od). In an RCT of patients who did not tolerate allopurinol 300 mg/day well or achieve target sUA, benzbromarone 200 mg/day was found to be more effective and better tolerated than probenecid 2 g/day [150], and benzbromarone 200 mg daily was approximately equipotent with allopurinol 600 mg/day in lowering sUA to target in another RCT [151]. All uricosurics are contraindicated or need to be used with great caution in patients with urolithiasis or severe renal impairment. Clinical experience indicates that sulfinpyrazone and probenecid have limited efficacy in patients with mild or moderate renal insufficiency (GFR $<$ 60 ml/min) but benzbromarone has been shown to maintain uricosuric efficacy when the GFR is as low as 20 ml/min [152]. Probenecid and benzbromarone are only available for the treatment of patients with gout in the UK on a named patient basis, and patients requiring these unlicensed drugs should be under the care of a rheumatologist. The use of benzbromarone was restricted in Europe following rare reports of severe hepatotoxicity, mainly from Asian countries. Patients treated with benzbromarone should have liver function tests monitored but the risk of serious hepatotoxicity in patients receiving the benzbromarone in Europe is estimated as approximately 1 in 17 000 [153].

(viii) Losartan and fenofibrate should not be used as a primary ULT but where treatment for hypertension or dyslipidaemia, respectively, is required, they may be considered as they have a weak uricosuric effect. Vitamin C supplements (500–1500 mg daily) also have a weak uricosuric effect. LoE: III; SOR: 89% (range 63–100%).

Rationale

Unlike ACE inhibitors, beta blockers and other angiotensin II receptor blockers used for treating hypertension, losartan 50 mg od has been shown to have mild uricosuric effects in patients with gout [154], and the use of losartan was associated with a significantly reduced risk of incident gout (RR = 0.81, 95% CI: 0.70, 0.94) in a large community-based UK case–control study using data from The Health Improvement Network [155].

The lipid-lowering agent fenofibrate has been shown to be uricosuric [156] and to have a modest additional urate-lowering effect in gout patients being treated with allopurinol [157, 158]. Losartan (50 mg od) and fenofibrate (300 mg od) were both found to have some additional urate-lowering efficacy when administered to gout patients receiving ULT with allopurinol or benzbromarone in one small study [159].

A meta-analysis of 13 RCTs found that sUA can be lowered by vitamin C supplementation in patients without gout and that sUA reductions were greater in trials administering vitamin C $>$500 mg/day [87]. A single RCT in patients with gout showed that vitamin C (500 mg/day for 8 weeks) reduced the sUA ($-$0.014 mmol/l) much less than allopurinol ($-$0.118 mmol/l) [88]. Vitamin C supplements in this modest dose only have a very weak uricosuric effect in people with gout, which is insufficient for it to be used as substitute monotherapy for allopurinol or other licensed ULT. Moreover, the study of Stamp suggests that in this dosage it is also unlikely to be a clinically useful adjunct to standard ULT with allopurinol [88]. No studies have been undertaken to assess whether vitamin C supplementation is effective in reducing the incidence of recurrent gout attacks.

(ix) A uricosuric agent can be used in combination with a xanthine oxidase inhibitor in patients who do not achieve a therapeutic serum urate target with optimal doses of monotherapy. LoE: III; SOR: 88% (range 71$-$100%).

Rationale

Enhancement of uric acid excretion and reduction of sUA in patients with tophaceous gout by combined treatment with sulfinpyrazone and allopurinol was first demonstrated nearly 50 years ago [160]. Observational studies by Perez-Ruiz and colleagues have shown that the velocity of tophus volume reduction in patients with chronic tophaceous gout could be accelerated with more profound reduction of sUA by combined treatment with allopurinol and benzbromarone [118]. They subsequently demonstrated that even gout patients that are primary overproducers of urate, with apparently increased urine uric acid excretion, also have evidence of defective fractional urate clearance [161] and may therefore respond to addition of a uricosuric drug if their sUA is not reduced to target levels with a xanthine oxidase inhibitor alone. More recent observational studies have also shown that combined treatment with allopurinol and benzbromarone was more effective in lowering sUA than either agent alone [162]. A recent single case report has demonstrated effective lowering of sUA in a patient with gout and chronic renal failure with addition of a combination of allopurinol and febuxostat to benzbromarone when combination of a single xanthine oxidase inhibitor with benzbromarone was ineffective [163]. Most recently phase III trials of a new selective uric acid reabsorption inhibitor, lesinurad, have shown it to be effective in doses of 200 mg od and 400 mg od in lowering the sUA to target levels in combination with allopurinol in patients with gout that have not responded adequately to allopurinol $\geqslant$300 mg daily ($\geqslant$200 mg in moderate renal impairment) [164]. Its use for this indication has recently been given FDA and EMA approval and marketing authorization.

(x) Colchicine 500 μg bd or od should be considered as prophylaxis against acute attacks resulting from initiation or up-titration of any ULT and continued

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for up to 6 months. In patients who cannot tolerate colchicine, a low-dose NSAID or coxib, with gastroprotection, can be used as an alternative providing there are no contraindications. LoE: Ib; SOR: 86% (range 29–100%).

Rationale

Prophylaxis against acute flares in patients initiating ULT has been the subject of two recent systematic reviews [125, 165]. There is more evidence from RCTs to support the use of colchicine, than for NSAIDs, for flare prophylaxis. In a 6-month placebo-controlled RCT in patients with gout receiving probenecid for ULT, the flare rate was reduced from 6 to 2.3 flares per annum in patients receiving colchicine 500 μg daily [166]. In another 6-month placebo-controlled RCT in patients initiating allopurinol at a dose of 100 mg od followed by up-titration in 100 mg increments, flares occurred in 33% of patients given colchicine 500 μg bd for flare prophylaxis compared with 77% of those treated with placebo [167]. An investigator-initiated reanalysis of gout flare data from the three phase III trials of febuxostat found that flare prophylaxis for up to 6 months with colchicine 600 μg od or naproxen 250 mg bd, during the initiation of ULT with febuxostat or allopurinol, appeared to provide greater benefit than flare prophylaxis for 8 weeks, with no increase in adverse events [168]. There is little other research evidence to help determine the optimal duration of prophylaxis. A systematic review [125] identified a single RCT comparing three treatment groups given colchicine 1000 μg daily for 3–6, 7–9 and 10–12 months [169]. By 12 months, recurrent acute gout was reported by 54%, 28% and 23%, respectively. Adverse events did not differ between the three groups. However, the risk of bias was high.

Long-term prophylaxis with colchicine or NSAIDs in patients with gout always demands a careful consideration of the overall benefit to risk balance in individual patients, and especially in those with co-morbidities and potential for drug interactions. When using Cox-2 selective or non-selective NSAIDs, the risks of upper GI bleeds and cardiovascular risk should be considered, and gastro-protection with a proton pump inhibitor is recommended. Although usually well tolerated, possible side effects of long-term colchicine include diarrhoea, nausea/vomiting, marrow suppression, myopathy and rhabdomyolysis.

The use of flare prophylaxis is particularly important when ULT is initiated with febuxostat, as the lowest available starting dose in the UK (80 mg) lowers the serum acid level to a greater degree than the starting dose of allopurinol (100 mg), and the risk of precipitating a gout flare is consequently greater [97].

There is no research evidence to support the use of corticosteroids for flare prophylaxis.

IL-1 inhibitors have also been investigated for use for flare prophylaxis [69, 169–172] but none are currently approved for this indication by the EMA or FDA and it is likely that the costs of these biologics will preclude their use for this indication in patients with gout in the UK NHS. In a phase II trial of various doses of canakinumab and colchicine 500 μg od in over 400 patients initiating treatment with allopurinol, the mean number of flares per patient after 4 months was less in the canakinumab-treated patients at all doses >50 mg but there was no evidence of a dose response and there were more infections in the canakinumab-treated patients (18%) than in those given colchicine prophylaxis (12%) [169].

Management points in special groups

Patients with renal insufficiency

CKD and nephrolithiasis are very common in patients with gout. A recent systematic review and meta-analysis of epidemiological and observational studies suggested that the overall prevalence of CKD (stage 3 or greater; GFR < 60 ml/min/1.73 m^2) in patients with gout was 24% compared with 8.5% in the non-gouty population, and the prevalence of self-reported nephrolithiasis was 14% [173]. This presents physicians with important challenges in managing patients with gout, and management of gout in patients with renal impairment has been the subject of two recent systematic reviews and a guideline from the US National Kidney Foundation [174, 175].

For the management of acute gout, the dose of oral colchicine should be reduced in patients with eGFR 10–50 ml/min/1.73 m^2 but is contraindicated in patients with more severe renal impairment (GFR < 10 ml/min/1.73 m^2). High-dose NSAIDs should not be used even in patients with moderate renal impairment [176, 177]. Although the efficacy of corticosteroids in those with CKD has not been evaluated in RCTs [174], clinical experience suggests that they can be effective and safe for managing acute gout in patients with severe renal impairment or in other patients in whom colchicine and NSAIDs cannot be used. Intra-articular triamcinolone hexacetonide (40 mg for large joints, 10–20 mg for smaller joints) is often recommended if only one or two joints are inflamed, or a 7–14-day course of oral prednisolone (30–40 mg tapering to nothing), if multiple joints are involved or if arthrocentesis is not possible.

Guidelines for the use of allopurinol, febuxostat and uricosuric drugs in patients with renal impairment have been discussed following recommendations V, VI and VII for the optimal use of urate-lowering therapies.

Flare prophylaxis with colchicine or NSAIDs in patients with gout and renal insufficiency initiating ULT needs to be undertaken with great caution as the risks of colchicine toxicity, especially myopathy, are increased in patients with renal impairment [178] and NSAIDs can cause acute kidney injury and further impair renal function in patients with CKD [179]. Prophylaxis with low-dosage colchicine, adjusted for renal function, is believed to be a safer option than low-dose NSAIDs [174, 175]. Based on pharmacokinetic data in patients with CKD [180], it is suggested that there is no need for reduction in colchicine dosage (500 μg od or bd) for flare prophylaxis in patients with mild renal insufficiency (eGFR >60 ml/min/1.73 m^2) but the dose should be limited to 500 μg od in those with an eGFR of 30–60 ml/min/1.73 m^2 and to 500 μg

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every 2–3 days with eGFR 10–30 ml/min/1.73 m^2 [181] and avoided altogether if eGFR <10 ml/min/1.73 m^2. Although it is usually recommended that NSAIDs should be avoided in all patients with renal impairment, a recent systematic review and meta-analysis of observational studies found no evidence of accelerated CKD progression in patients with moderate to severe renal impairment treated with low-dose NSAIDs (OR: 0.96; 95% CI: 0.86, 1.07) [176].

Severe refractory tophaceous gout

Patients with severe symptomatic tophaceous gout in whom hyperuricaemia cannot be controlled with standard ULTs alone, or in combination, should be referred to a rheumatologist. Pegloticase, a polyethylene glycol modified mammalian uricase, can be effective in such patients [182, 183], although not approved by NICE. The drug is administered by i.v. infusion (8 mg in 250 ml normal saline over 2 h) every 2 weeks by physicians with experience and facilities for dealing with infusion reactions, and patients should be pre-treated with antihistamines and steroids to reduce the risk of infusion reactions, in addition to low-dose colchicine or NSAIDs for flare prophylaxis. Despite heavy pegylation, pegloticase is immunogenic. sUA should be measured before each infusion, and treatment discontinued if the sUA is >360 μmol/l as transient responders (about 50%) appear to be at increased risk for infusion reactions and anaphylaxis. Pegloticase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because of the risk of haemolysis, and extra caution is required in patients with congestive heart failure. Pegloticase has FDA approval and EMA marketing authorization in Europe but has not been approved by NICE or the SMC because of concerns about toxicity and cost. Rasburicase, a recombinant *Aspergillus flavus* uricase that is licensed for the treatment and prophylaxis of tumour lysis syndrome, but not for gout, has also been used successfully in some patients with severe refractory gout [184] despite its greater potential immunogenicity. Prescribers in the UK should be aware of the potential need to obtain approval for an individual funding request before these drugs should be used.

In pregnancy

Apart from patients with familial juvenile hyperuricaemic nephropathy [185], gout is very uncommon in pre-menopausal women and in pregnancy [186] and so data are sparse. Conservative measures including ice are safe for managing acute attacks. NSAIDs can be used in the mid-trimester [187]. Steroids are generally safe to use in pregnancy [188] and the recommendations for lifestyle modifications including the dietary changes discussed previously are also safe.

The safety data for colchicine during pregnancy are largely derived from studies of its use in FMF [189] although there are also some reports of chromosomal damage. High concentrations of colchicine can be found in breast milk and so colchicine is best avoided when breast feeding.

Allopurinol and febuxostat have not been adequately tested during pregnancy. Probenecid was used extensively in the past during antibiotic treatment of infections in pregnant women without any reported fetal toxicity.

Applicability and utility

Statement of potential organizational barriers to introduction

Despite the increasing prevalence of gout and the availability of effective and potentially curative ULT for >50 years, its management remains poor with only 40% of patients with gout ever receiving ULT [1]. Inadequate provision of information to patients [29] has been identified as one of the key barriers [30–32] to effective management of gout. There is preliminary evidence that patient adherence to ULT and lowering of sUA to target levels can be achieved with better provision of information and a package of care based on guideline recommendations [33]. Effective provision of information and monitoring of treatment to achieve target sUA levels requires regular ongoing clinical review. However, anecdotal reports suggest that some secondary care organizations prohibit follow-up of patients with gout, insisting on discharge with a treatment plan to primary care where treatment is known to be suboptimal. Furthermore, although ~20% of people presenting with their first attack will have a second episode within 12 months [190], patients often do not consult for subsequent attacks, so practitioners may not be aware of recurrent attack frequency and the need for ULT, highlighting the case for discussing ULT early in the course of disease.

Potential cost implications for implementation of the guideline

Although there are few cost-effectiveness studies in gout, the guideline takes these into account. The guideline recommends as the first-line ULT allopurinol, which is inexpensive and likely to be tolerated and effective in the vast majority of patients with gout. The cost-effectiveness of febuxostat as a second-line ULT has been established and our guidance for its use concords with its NICE and SMC approval [129, 130, 144, 146]. The guideline does include recommendations for unlicensed or non-NICE-approved use of pegloticase and IL-1 inhibitors although the need to use these drugs is likely to be rare and individual clinicians are advised to consider local arrangements for funding individual funding requests if using these drugs.

Summary of changes in the revised recommendations

This guideline contains several important changes from the 2007 BSR/BHPR guideline [2]. The importance of patient education and provision of information about gout and its treatment are strongly emphasized in the updated guideline (recommendation I for the management of acute attacks, recommendations II and III for the modification of

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lifestyle and risk factors and recommendation I, II and III for the optimal use of urate-lowering therapies). It is now recommended that an NSAID or colchicine are both drugs of choice for acute gout when there are no contraindications and that the choice of first-line agent should be determined by renal function, co-morbidities and patient preference (recommendation III for the management of acute attacks). Combinations of NSAIDs with corticosteroids or colchicine can be used for acute attacks where response to monotherapy is insufficient (recommendation V for the management of acute attacks), and IL-1 inhibitors may be considered in patients who have not responded adequately to standard treatment (recommendation VI for the management of acute attacks).

The revised guideline emphasizes that all patients with gout should be screened for cardiovascular risk factors and co-morbid conditions such as cigarette smoking, hypertension, diabetes mellitus, dyslipidaemia, obesity and renal disease at least annually and treated appropriately (recommendation V for the modification of lifestyle and risk factors). It is now recommended that that the option of ULT should be explained and offered to all patients with gout as part of their education about the condition and that patients are fully involved in the decision as to when to commence ULT (recommendations I and II for the optimal use of urate-lowering therapies). Although the revised guideline still recommends reduction of sUA with ULT to a target of 300 μmol/l, ULT dose adjustment to the less stringent sUA target of 360 μmol/l is now recommended after some years of successful ULT when tophi have resolved and the patient remains symptom free (recommendation IV for the optimal use of urate-lowering therapies). It is now recommended that in patients with renal impairment the maintenance dose of allopurinol need not be strictly limited according to the creatinine clearance. The starting dose should, however, be low and then carefully increased with smaller increments (50 mg) until the target sUA of 300 μmol/l is reached (recommendation V for the optimal use of urate-lowering therapies). Febuxostat can be used as an alternative second-line xanthine oxidase inhibitor for patients in whom allopurinol is not tolerated or whose renal impairment prevents allopurinol dose escalation sufficient to achieve the therapeutic target (recommendation VI for the optimal use of urate-lowering therapies). For patients with severe symptomatic tophaceous gout in whom hyperuricaemia cannot be controlled with standard ULTs alone, or in combination, treatment with pegloticase can be considered by physicians with experience and facilities for dealing with infusion reactions.

An audit tool is available on the website of the British Society for Rheumatology. Questions for audit and recommendations for future clinical research can be found Supplementary Table S2, available at *Rheumatology online* and in the audit tool.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.
Disclosure statement: W.Z. reports grants from Arthritis Research UK, Health Technology Assessment, National Institute for Health Research and honoraria for consultations from AstraZenica, Daiichi Sankyo, Biobarica, Hisun and Grunenthal outside the submitted work. M.D. has received honoraria for ad hoc advisory boards relating to osteoarthritis and gout from Ardea Biosciences, AstraZeneca, Nordic Biosciences and Roche; AstraZeneca are funding a Nottingham University investigator-led non-drug study on gout. G.N. was a member of the Independent Disease Monitoring Committee for trials of lesinurad (Ardea/AstraZeneca), and has received honoraria for advisory boards from Gruenenthal and Menarini, and research funding from Menarini for the FAST trial. T.M.M. is or has been principle investigator on trials paid for by Pfizer, Novartis, Ipsen, Teijin and Menarini, received consulting or speakers fees from Pfizer, Novartis, Takeda, Shire and Lundbeck and their department holds research grants from Novartis, Pfizer, Amgen, Ipsen, Teijin and Menarini. K.M.J. has received educational sponsorship and funding for UK Gout Society in capacity as Trustee. G.J.D. has received ad hoc advisory board honoraria from AstraZeneca. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 10, October 2015, pp 2557–2568
DOI 10.1002/art.39254
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SPECIAL ARTICLE

2015 Gout Classification Criteria

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

The American College of Rheumatology is an independent, professional, medical and scientific society which does not guarantee, warrant, or endorse any commercial product or service.

This article is published simultaneously in the October 2015 issue of *Annals of the Rheumatic Diseases*.

Supported jointly by the American College of Rheumatology and the European League Against Rheumatism. Dr. Neogi's work was supported by the NIH (grants P60-AR-47785 and K23-AR-055127). Dr. Singh's work was supported by the NIH (grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Aging, and the National Cancer Institute) and the Agency for Healthcare Research and Quality (Center for Education and Research on Therapeutics program). Dr. Taylor's work was supported by Arthritis New Zealand.

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Objective. **Existing criteria for the classification of gout have suboptimal sensitivity and/or specificity, and were developed at a time when advanced imaging was not available. The current effort was undertaken to develop new classification criteria for gout.**

Methods. **An international group of investigators, supported by the American College of Rheumatology and the European League Against Rheumatism, conducted a systematic review of the literature on advanced imaging of gout, a diagnostic study in which the presence of monosodium urate monohydrate (MSU) crystals in synovial fluid or tophus was the gold standard, a ranking exercise of paper patient cases, and a multicriterion decision analysis exercise. These data formed the basis for developing the classification criteria, which were tested in an independent data set.**

Results. **The entry criterion for the new classification criteria requires the occurrence of at least 1 episode of peripheral joint or bursal swelling, pain, or tenderness. The presence of MSU crystals in a symptomatic joint/bursa (i.e., synovial fluid) or in a tophus is a sufficient criterion for classification of the subject as having gout, and does not require further scoring. The domains of the new classification criteria include clinical (pattern of joint/bursa involvement, characteristics and time course of symptomatic episodes), laboratory (serum urate, MSU-negative synovial fluid aspirate), and imaging (double-contour sign on ultrasound or urate on dual-energy computed tomography, radiographic gout-related erosion). The sensitivity and specificity of the criteria are high (92% and 89%, respectively).**

Conclusion. **The new classification criteria, developed using a data-driven and decision analytic approach, have excellent performance characteristics and incorporate current state-of-the-art evidence regarding gout.**

Introduction

Gout, which is characterized by deposition of monosodium urate monohydrate (MSU) in synovial fluid and other tissues, is the most common form of inflammatory arthritis, with a prevalence of 3.9% in the US (1), 0.9% in France (2,3), 1.4–2.5% in the UK (4–6), 1.4% in Germany (5), and 3.2% (European ancestry)–6.1% (Maori ancestry) in New Zealand (7). Over the last decade, several new therapies for gout have been approved by regulatory agencies or are being tested (8). The conduct of trials that lead to drug approval, and of observational studies that provide insights into risk factors, genetic associations, and general epidemiology of gout, is critically dependent on appropriate identification of individuals with gout for inclusion in such studies. Classification criteria serve the purpose of enabling standardized assembly of a relatively homogeneous group of individuals with the disease of interest for enrollment into such studies (9).

There are several existing sets of classification criteria or diagnostic rules for gout (10–14), with the most widely used being the 1977 American Rheumatism Association (now the American College of Rheumatology [ACR]) preliminary criteria for the classification of the acute arthritis of primary gout (10). These preliminary criteria were intended for identifying the acute arthritis of gout and not necessarily for intercritical gout, the spectrum of comparator diseases was limited, and physician diagnosis was the gold standard. In a recent study in which the gold standard was MSU crystal status in synovial fluid or nodule aspirate among individuals with a broad range of diagnoses, the sensitivity of existing criteria sets (10–14) ranged from 57.6% to

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Submitted for publication December 15, 2014; accepted in revised form June 18, 2015.

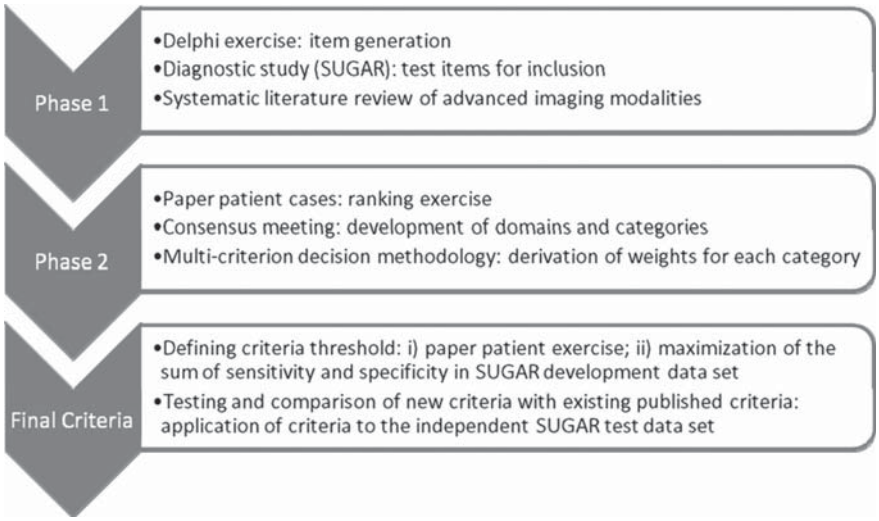
Phase 1
•Delphi exercise: item generation
•Diagnostic study (SUGAR): test items for inclusion
•Systematic literature review of advanced imaging modalities
Phase 2
•Paper patient cases: ranking exercise
•Consensus meeting: development of domains and categories
•Multi-criterion decision methodology: derivation of weights for each category
Final Criteria
•Defining criteria threshold: i) paper patient exercise; ii) maximization of the sum of sensitivity and specificity in SUGAR development data set
•Testing and comparison of new criteria with existing published criteria: application of criteria to the independent SUGAR test data set

Figure 1. Flow chart of the study process. The major steps taken to develop the new American College of Rheumatology/European League Against Rheumatism criteria for classification of gout are outlined. SUGAR = Study for Updated Gout Classification Criteria.

100% (i.e., 100% with MSU crystal identification as sufficient for classification as gout), whereas the specificity ranged from 34.3% to 86.4%, with no single criteria set having both excellent sensitivity and excellent specificity (15,16). Such findings highlight the need for classification criteria with improved performance characteristics, with higher specificity likely to be favored in order to ensure that individuals enrolled into trials for treatments with unclear efficacy and safety truly have gout.

Accurate classification of gout without crystal documentation for recruitment into studies is also needed, since the majority of cases of gout are managed in primary or acute care settings (17,18), where synovial fluid aspiration and polarizing microscopy are not commonly performed. Additionally, the existing published criteria were developed at a time when advanced imaging modalities, such as ultrasonography or dual-energy computed tomography (DECT), had not been studied; their utility for gout classification in the context of other clinical and laboratory parameters is not known.

To address these issues, an international collaborative working group to develop new classification criteria for gout was convened with the support of the ACR and the European League Against Rheumatism (EULAR) (19). The final results are reported here.

Methods

The major steps taken to develop the new classification criteria are outlined in Figure 1.

Phase 1. To identify factors to be considered for the content of classification criteria for gout, 3 studies were undertaken (Figure 1). First, clinicians with expertise in gout and patients with gout identified factors they believed to discriminate gout from other rheumatic diseases in a Delphi exercise (20). Second, we tested items from this Delphi exercise that were agreed to be potentially discriminatory for gout and items from existing classification criteria in a cross-sectional diagnostic study (Study for Updated Gout Classification Criteria [SUGAR]) (21). Briefly, this study included 983 consecutive subjects (exceeding the recruitment target of 860) who had had joint swelling or a subcutaneous nodule within the previous 2 weeks, either of which was judged to be conceivably due to gout. These subjects were recruited from rheumatology clinics in 16 countries. All subjects were required to undergo aspiration of the symptomatic joint or nodule, with crystal examination performed by a certified observer (21,22), and imaging (ultrasound, radiography). Those who were MSU crystal positive were designated as cases while those who were MSU crystal negative were designated as controls, irrespective of clinical diagnosis. Analyses in the SUGAR study were conducted among two-thirds of the sample (derivation data set; n = 653); the other one-third (n = 330) were analyzed as the validation data set for the final criteria. Third, we conducted a systematic literature review of advanced imaging modalities for classifying gout (23).

Phase 2. *Rationale.* It was recognized that the SUGAR study and the imaging review may have some limitations. The SUGAR study might have been prone to selection bias as MSU crystal positivity was required in order for a subject to be considered a case; this may have introduced bias toward larger joints, more severe disease, and/or tophaceous disease. In addition, subjects were recruited from rheumatology clinics, which may have contributed to spectrum bias since most patients with gout are seen in primary care settings. The systematic literature review of imaging was limited by the relative paucity of published data, and comparator diseases included were limited. Thus, Phase 2 was envisioned as a complementa-

ry phase that would incorporate the data derived in Phase 1 with clinical expertise to address a broader spectrum of clinical gout.

Approach to identifying domains and categories. In Phase 2, an international panel of expert rheumatologists and primary care physicians used a multicriterion decision analytic consensus methodology, informed by data generated in Phase 1, to determine the factors that best discriminated gout from other rheumatic diseases that could conceivably be considered in the differential diagnosis. Such an approach would lead to expert-derived, data-informed weighting of discriminating factors. The specific methods are described below.

Rheumatologists and general internists with an interest in gout submitted paper patient cases of patients for whom gout was in the differential diagnosis, using standardized data collection forms. A subset of 30 paper patient cases was selected to represent a broad spectrum of the probability of gout. Prior to the in-person expert panel meeting, panel members were given the data from Phase 1 to review, and they were asked to rank-order the 30 paper patient cases from lowest to highest probability of having gout.

At the in-person expert panel meeting, held over 2 days (June 9–10, 2014 in Paris, France in advance of the EULAR Congress), 3 concepts were agreed upon a priori. First, the task was to develop criteria that would enable standardized assembly of a well-defined, relatively homogeneous group of subjects representative of persons with gout, for entry into observational studies or clinical trials. Such criteria are not intended to capture *all* possible patients, but rather to capture the great majority of patients with shared key features of gout. Second, the classification was to apply to the patient's total disease experience, not to classify individual symptomatic episodes. Third, elements of the criteria could be accrued over time such that individuals could fulfill criteria at a later time point even if they did not at the initial assessment.

Review of the Phase 1 data and the paper patient case ranking exercise formed the basis for in-depth discussion to identify key features that were pertinent to the probability of gout. Based on these key features, initial formulation of potential criteria was developed, with consideration of entry, sufficient, and exclusion criteria, and more precise definition of domains and their categories. Decisions regarding domains and their categories were supported, where possible, by Phase 1 data and/or any other available published evidence.

Approach to assigning relative weights to domains and categories. Once the Paris panel agreed upon preliminary domains and categories, the members undertook a discrete-choice conjoint analysis exercise guided by an experienced facilitator (RPN) and aided by a rheumatologist with experience in the process (TN), similar to that used for other classification criteria (e.g., rheumatoid arthritis, systemic sclerosis) (24–29). Specifically, we used a computer software program, 1000Minds (www.1000minds.com), which utilizes decision science theory and computer adaptive technology to carry out a series of discrete forced-choice experiments through pairwise ranking of alternatives that lead to quantified weights of each domain and each category within the domains (28,30). Briefly, the expert panel was presented with a series of paired scenarios, each of which contained the same 2 domains, but with different combination of the domains' categories grouped together in each scenario. The panel was instructed to assume that all other parameters were equivalent between the 2 patients represented by the scenarios. The distribution of votes (percent who voted for "A," "B," or "equal probability") was presented for each pair of scenarios after each vote. Discussion occurred after each vote, with re-voting as necessary. Consensus was considered to have been achieved when all participants either indicated complete agreement as to which scenario represented a higher probability of gout, or indicated that they could accept the majority opinion.

Relative weights were derived with the decision analytic software, based on the voting results of the discrete-choice scenarios and refined by each successive result. Upon completion of the voting exercise, the relative weights for each category and domain, and the face validity of the resulting rank order of 10 paper patient cases, were reviewed.

After the in-person meeting, minor scoring simplifications were incorporated and pretested in the SUGAR derivation data set (i.e., the original two-thirds sample analyzed in Phase 1). A cutoff score that maximized the sum of sensitivity and specificity was determined, to examine misclassification.

Approach to developing final criteria scoring. The raw weights from the scoring system were simplified into whole numbers, with performance characteristics assessed for each simplification.

Approach to defining criteria threshold for classifying gout. The original 30 paper patient cases (except for 3 with demonstrated MSU crystals), in addition to 20 subjects from the SUGAR study analyzed in Phase 1 who had unique scores close to the cutoff score derived as described above, were used for a threshold identification exercise. For these 20 subjects, if synovial fluid microscopy had failed to show MSU crystals, this information was provided. Otherwise, the results of synovial fluid examination were recorded as "not done." This information was not made known to the expert panel. These cases were arranged according to their score in descending order. In an online exercise, the expert panel indicated whether they would classify the patient as having gout with sufficient confidence to feel comfortable enrolling that patient into a Phase 3 trial of a new urate-lowering agent.

Testing of the new gout classification criteria and comparison with existing published criteria. The final criteria set was evaluated in the SUGAR validation data set (i.e., the one-third of the data set that had not been used for any analyses to date [n = 330]); the purpose of this was to enable validation of the newly developed criteria in an independent data set. A secondary analysis was conducted to evaluate how the criteria would perform if only clinical parameters were available (i.e., without MSU determination or imaging). The performance characteristics of the new criteria were compared with those of existing published criteria using logistic regression.

Results

The expert panel (n = 20) comprised 19 physicians with a clinical and/or research interest in gout (17 clinical rheumatologists and 2 primary care physicians) and an epidemiologist/biostatistician; 9 members of the panel were from the US, 8 from Europe, 2 from New Zealand, and 1 from Mexico. One hundred thirty-three paper cases were submitted by the expert panel and 79 clinical rheumatologists and general internists.

Table 1. Definitions and considerations for each domain*

Domain†	Definitions and special considerations
1. Pattern of joint/bursa involvement during symptomatic episode(s) ever Categories are defined as per the description of the distribution of joints involved	Distribution of joints: involvement (ever) of i) Joint(s) or bursa(e) other than ankle, midfoot or first metatarsophalangeal (MTP) joint (or their involvement only as part of a polyarticular presentation) ii) Ankle or midfoot joint(s) as monoarticular or part of an oligoarticular presentation without first MTP joint involvement iii) MTP joint involvement as monoarticular or part of an oligoarticular presentation
2. Characteristics of symptomatic episode(s) ever Categories are defined as No characteristics present 1 characteristic present 2 characteristics present 3 characteristics present	Characteristics to consider: presence (ever) of i) Great difficulty with walking or inability to use the affected joint(s) during a symptomatic episode ever (patient-reported) ii) Can't bear touch or pressure to the affected joint during a symptomatic episode ever (patient-reported) iii) Erythema overlying affected joint during a symptomatic episode ever (patient-reported or physician-observed)
3. Time course of symptomatic episode(s) ever Categories are defined as No typical episodes 1 typical episode Recurrent typical episodes	"Typical symptomatic episode": presence (ever) of >2 of the following, irrespective of antiinflammatory treatment i) Time to maximal pain <24 hours ii) Resolution of symptoms in ≤14 days iii) Complete resolution (to baseline level) between symptomatic episodes
4. Clinical evidence of tophus Categories are defined as Present Absent	Appearance: draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity (Figure 2) Location: classic locations—joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)
5. Serum urate level, off-treatment Categories are defined as <4 mg/dl (0.24 mmoles/liter) 4–<6 mg/dl (0.24–<0.36 mmoles/liter) 6–<8 mg/dl (0.36–<0.48 mmoles/liter) 8–<10 mg/dl (0.48–<0.60 mmoles/liter) ≥10 mg/dl (≥0.60 mmoles/liter)	Which serum urate measurement to use: highest reading on record, off urate-lowering therapy Special considerations: Ideally, the serum urate level should be scored if tested at a time when the patient was not receiving urate-lowering therapy and it was >4 weeks from the start of an episode; *if* practicable, retest under those conditions. If serum urate level is ≥10 mg/dl, no need to retest.
6. Synovial fluid analysis Categories are defined as MSU negative Not done	Location: symptomatic (ever) joint or bursa Special considerations: Assessment should be performed by a trained observer. Note: MSU positive is a sufficient criterion.
7. Imaging evidence of urate deposition Categories are defined as Absent *or* not done Present (either modality)	Modality: ultrasound or DECT Appearance: double-contour sign on ultrasound (Figure 3A)‡ *or* urate deposition on DECT (Figure 3B)§ Location: symptomatic (ever) joint or bursa
8. Imaging evidence of gout-related joint damage Categories are defined as Absent *or* not done Present	Modality: radiography Appearance of gout-related erosion: cortical break with sclerotic margin and overhanging edge; excludes gull wing appearance (Figure 3C) Location: radiograph of hands and/or feet; excludes distal interphalangeal joints

* Symptomatic (ever) refers to pain and/or swelling.
† Categories within each domain are hierarchical; if a subject fulfills more than 1 category, the highest category should be selected.
‡ A false-positive double-contour sign (artifact) may appear at the cartilage surface, but should disappear with a change in the insonation angle of the probe (31,32).
§ Images should be acquired using a dual-energy computed tomography (DECT) scanner, with data acquired at 80 kV and 140 kV and analyzed using gout-specific software with a 2-material decomposition algorithm that color-codes urate (33). A positive scan result is defined as the presence of color-coded urate at articular or periarticular sites. Nailbed, submillimeter, skin, motion, beam hardening, and vascular artifacts should not be interpreted as DECT evidence of urate deposition (34).

Based on review of the Phase 1 data and the ranking exercise with the 30 cases representing low to high probability of gout, initial key factors that were identified as being important for classifying gout were presence of MSU crystals, pattern of joint involvement, intensity of symptomatic episodes, time to maximal pain and to resolution, episodic nature of symptoms, presence of clinical tophus, level of serum urate, imaging features, response to treatment, family history, and risk factors or associated comorbidities. The last 3 factors were not considered further as they are not features of gout itself despite their association with gout, and inclusion of risk factors or

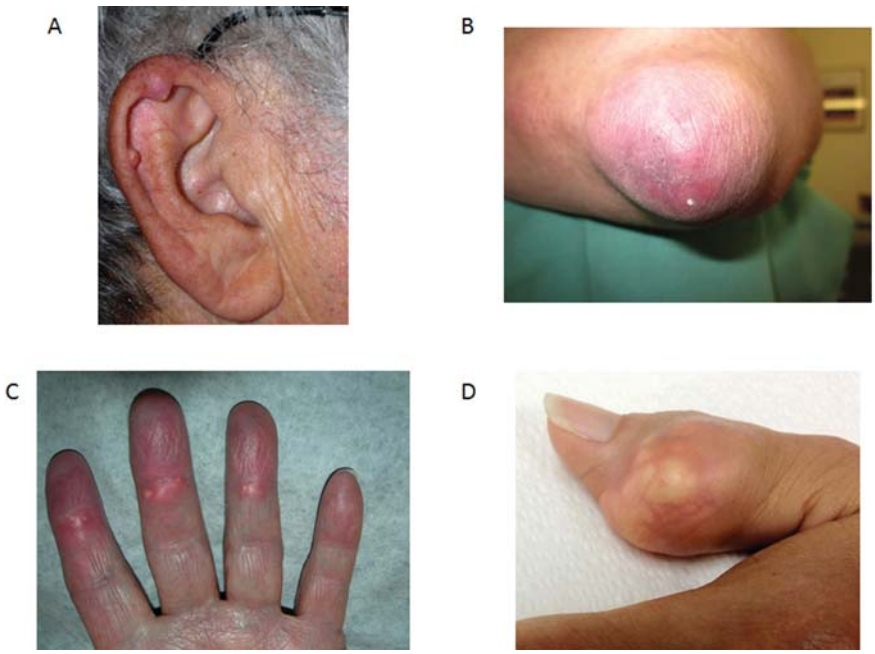

Figure 2. Examples of tophus. The tophus is defined as a draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity. Typical locations are the ear (**A**), the elbow (olecranon bursa) (**B**), and the finger pulps (**C** and **D**). Note the overlying vascularity in **D**.

comorbidities in the definition of gout would preclude future studies evaluating their association with gout.

Entry, sufficient, and exclusion criteria. Before embarking upon defining domains and domain categories (the classification criteria), we defined entry, sufficient, and exclusion criteria. The entry criteria were intended to be used to identify the relevant patient population to whom the classification criteria would be applied. Sufficient criteria were intended to define features such as a gold standard that alone could classify gout without further need to apply the classification criteria scoring system. Exclusion criteria were intended to define individuals in whom gout could be ruled out (among those who met entry criteria) and to whom the classification criteria should not be further applied. The expert panel agreed that these classification criteria should be applicable only to people with symptomatic disease because the prognosis of asymptomatic disease is presently not well delineated in the literature, and to enable categorization based on features of symptomatic episodes. The *entry criterion* was defined as the occurrence of at least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa. The *sufficient criterion* was defined as the presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus as observed by a trained examiner. The panel agreed that there would be no exclusion criteria because gout can often coexist with other diseases and because synovial fluid microscopy can sometimes fail to disclose MSU crystals in patients with gout for technical, sampling, or treatment reasons.

Domains and categories. Based on the key features identified initially, Phase 1 data, and available published literature, and with a defined population to whom the criteria would apply, the expert panel further developed the pertinent domains and their respective categories in an iterative process. The expert panel aimed to define relevant clinical and imaging parameters to be as specific as possible for gout.

The domains included clinical parameters (numbers 1–4), laboratory parameters (numbers 5 and 6), and imaging parameters (numbers 7 and 8). The specific domains and their respective definitions are summarized in Table 1. The domains were designed to be scored based on the totality of the subjects' symptomatic disease experience. All of the categories within domains are hierarchical and mutually exclusive, such that if both a higher and a lower category have been fulfilled at different points in time, the higher one should be scored; the highest categories are listed last within each domain.

Symptomatic episodes were defined as those in which there was swelling, pain, or tenderness in a peripheral joint or bursa. For the pattern of joint involvement, it was agreed that first metatarsophalan-

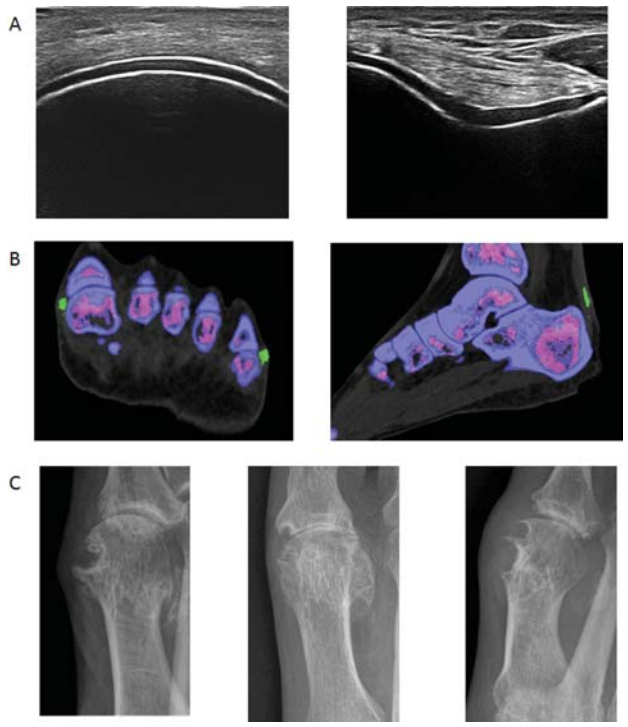

Figure 3. Examples of imaging features included in the classification criteria. **A,** Double-contour sign seen on ultrasonography. Left panel shows a longitudinal ultrasound image of the femoral articular cartilage; right panel shows a transverse ultrasound image of the femoral articular cartilage. Both images show hyperechoic enhancement over the surface of the hyaline cartilage (images kindly provided by Dr. Esperanza Naredo, Hospital Universitario Gregorio Marañon, Madrid, Spain). **B,** Urate deposition seen on dual-energy computed tomography. Left panel shows urate deposition at the first and fifth metatarsophalangeal joints; right panel shows urate deposition within the Achilles tendon. **C,** Erosion, defined as a cortical break with sclerotic margin and overhanging edge, seen on conventional radiography of the first metatarsophalangeal joint.

geal joint, ankle, or midfoot involvement as part of a polyarticular presentation, though possible in gout, was not specific enough for gout since that pattern could be seen commonly in other disorders such as rheumatoid arthritis. The time course of symptomatic episodes was to be considered irrespective of antiinflammatory treatment. For clinical tophus, a precise definition in terms of appearance and location was developed to assist in differentiation from other subcutaneous nodules that may be confused with tophi. Examples of clinically evident tophi are provided in Figure 2. Serum urate was considered a mandatory element of the classification criteria scoring system (i.e., the score cannot be computed without a serum urate value). For the synovial fluid domain, the fluid must be aspirated from a symptomatic (ever) joint or bursa, and assessed by a trained observer. If the synovial fluid aspirate was MSU positive, the individual would have been classified as having gout under the sufficient criterion without evaluating the rest of the classification criteria.

For imaging evidence of urate deposition, the imaging modalities with sufficient published data and investigator experience to support their utility in identifying urate deposition accurately were ultrasound and DECT. Magnetic resonance imaging and conventional CT did not have sufficient published data or investigator experience to support their consideration. For ultrasound evidence of urate deposition, the required finding is the double-contour sign (DCS), defined as hyperechoic irregular enhancement over the surface of the hyaline cartilage that is independent of the insonation angle of the ultrasound beam (note: false-positive DCS [artifact] may appear at the cartilage surface but should disappear with a change in the insonation angle of the probe) (31,32). Examples of gout-related DCS are provided in Figure 3. For DECT, urate deposition is defined as the presence of color-coded urate at articular or periarticular sites (Figure 3). Images should be acquired using a DECT scanner, with data acquired at 80 kV and 140 kV and analyzed using gout-specific software with a 2-material decomposition algorithm that color-codes urate (33). A positive scan result is defined as the presence of color-coded urate at articular or periarticular sites. Nailbed, submillimeter size, skin, motion, beam hardening, and vascular artifacts should not be interpreted as DECT evidence of urate deposition (34). The scoring of this imaging domain is applicable only to a symptomatic (ever) joint or bursa (i.e., swelling, pain, or tenderness), and is scored as present on either modality, or absent/not done (i.e., neither modality was performed). That is, if *either* imaging modality demonstrates the required finding, then urate deposition is considered to be present.

Finally, imaging evidence of gout-related joint damage is to be scored on the basis of conventional radiography of the hands and/or feet demonstrating at least 1 gout-related erosion, which is defined as a cortical break with sclerotic margin and overhanging edge (Figure 3). The distal interphalangeal joints and gull wing appearance should be excluded from this evaluation since they can occur in osteoarthritis.

Assigning relative weights to domains and categories. Once the domains and categories were defined, the expert panel undertook a series of discrete-choice experiments. This work resulted in weights being assigned to each category and domain, such that the highest category of each domain summed to a total of 100%. Any necessary revisions to the categories were

Table 2. The ACR/EULAR gout classification criteria*

	Categories	Score
Step 1: Entry criterion (only apply criteria below to those meeting this entry criterion)	At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa	
Step 2: Sufficient criterion (if met, can classify as gout without applying criteria below)	Presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus	
Step 3: Criteria (to be used if sufficient criterion not met)		
Clinical		
Pattern of joint/bursa involvement during symptomatic episode(s) ever†	Ankle *or* midfoot (as part of monoarticular or oligoarticular episode without involvement of the first metatarsophalangeal joint	1
	Involvement of the first metatarsophalangeal joint (as part of monoarticular or oligoarticular episode)	2
Characteristics of symptomatic episode(s) ever		
• Erythema overlying affected joint (patient- reported or physician-observed)	One characteristic	1
• Can't bear touch or pressure to affected joint	Two characteristics	2
• Great difficulty with walking or inability to use affected joint	Three characteristics	3
Time course of episode(s) ever		
Presence (ever) of ≥2, irrespective of antiinflammatory treatment:		
• Time to maximal pain <24 hours	One typical episode	1
• Resolution of symptoms in ≤14 days	Recurrent typical episodes	2
• Complete resolution (to baseline level) between symptomatic episodes		
Clinical evidence of tophus (Figure 2)		
Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)	Present	4
Laboratory		
Serum urate: Measured by uricase method.		
Ideally should be scored at a time when the patient was not receiving urate-lowering treatment and it was >4 weeks from the start of an episode (i.e., during intercritical period); *if* practicable, retest under those conditions. The highest value irrespective of timing should be scored.	<4 mg/dl (<0.24 mmoles/liter)‡	−4
	6–8 mg/dl (0.36–<0.48 mmoles/liter)	2
	8–<10 mg/dl (0.48–<0.60 mmoles/liter)	3
	≥10 mg/dl (≥0.60 mmoles/liter)	4
Synovial fluid analysis of a symptomatic (ever) joint or bursa (should be assessed by a trained observer)§	MSU negative	−2
Imaging (Figure 3)¶		
Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: ultrasound evidence of double-contour sign# *or* DECT demonstrating urate deposition**	Present (either modality)	4
Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrates at least 1 erosion††	Present	4

* A web-based calculator can be accessed at: http://goutclassificationcalculator.auckland.ac.nz, and through the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) web sites.

† Symptomatic episodes are periods of symptoms that include any swelling, pain, and/or tenderness in a peripheral joint or bursa.

‡ If serum urate level is <4 mg/dl (<0.24 mmoles/liter), *subtract 4 points*; if serum urate level is ≥4−<6 mg/dl (≥0.24−<0.36 mmoles/liter), score this item as 0.

§ If polarizing microscopy of synovial fluid from a symptomatic (ever) joint or bursa by a trained examiner fails to show monosodium urate monohydrate (MSU) crystals, *subtract 2 points*. If synovial fluid was not assessed, score this item as 0.

¶ If imaging is not available, score these items as 0.

Hyperechoic irregular enhancement over the surface of the hyaline cartilage that is independent of the insonation angle of the ultrasound beam (note: false-positive double-contour sign [artifact] may appear at the cartilage surface but should disappear with a change in the insonation angle of the probe) (31,32).

** Presence of color-coded urate at articular or periarticular sites. Images should be acquired using a dual-energy computed tomography (DECT) scanner, with data acquired at 80 kV and 140 kV and analyzed using gout-specific software with a 2-material decomposition algorithm that color-codes urate (33). A positive scan is defined as the presence of color-coded urate at articular or periarticular sites. Nailbed, submillimeter, skin, motion, beam hardening, and vascular artifacts should not be interpreted as DECT evidence of urate deposition (34).

†† Erosion is defined as a cortical break with sclerotic margin and overhanging edge, excluding distal interphalangeal joints and gull wing appearance.

Table 3. Performance of the gout classification criteria in the Study for Updated Gout Classification Criteria validation data set, in comparison with existing published criteria

Criteria set (ref.)	Area under the curve*	Sensitivity at published threshold	Specificity at published threshold
ACR/EULAR criteria	0.95	0.92	0.89
ACR/EULAR criteria (clinical-only)†	0.89	0.85	0.78
ACR 1977 criteria (full) (9)	0.83	1.00‡	0.51‡
ACR 1977 (survey) (9)	0.83	0.84‡	0.62‡
Rome (12)	0.95	0.97	0.78‡
Rome (clinical) (12)	NA	0.77‡	0.78‡
New York (13)	0.83	1.00‡	0.78‡
New York (clinical) (13)	NA	0.79‡	0.78‡
Mexico (11)	0.84	1.00‡	0.44‡
Mexico (clinical) (11)	NA	0.95	0.44‡
Netherlands (10)§	0.87	0.95	0.59‡

* Based on the sum of the number of items present, or the total score in the case of weighted criteria (American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] criteria and Netherlands criteria). NA = not applicable.
† Without synovial fluid microscopy or imaging.
‡ $P < 0.05$ versus the ACR/EULAR criteria.
§ The Netherlands criteria set was intended as a diagnostic aid, and has 2 possible cutoffs (see Supplementary Table 1, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39254/abstract); we used the higher cutoff for these analyses because such a score is deemed to suggest gout.

made with subsequent repetition of the discrete-choice experiments after any such changes.

A sample of 10 paper patient cases (from among the original 30 paper cases) was scored and rank-ordered with this preliminary scoring system. The cases were accurately ranked with reference to the expert panel's premeeting rankings, lending face validity to this preliminary scoring system. The scoring was also repeated without the imaging domains, which resulted in little change in the rank-ordering. Correlation between premeeting mean ranking and the initial scoring system ranking was high ($r^2 = 0.71$).

Defining criteria threshold for classifying gout. Using a cutoff score that maximized the sum of sensitivity and specificity from the SUGAR data, the percentage of false-negatives and false-positives was 13.9% and 10.5%, respectively. Next, the expert panel performed a threshold identification exercise designed to assess the members' willingness to enroll 47 paper cases, based on having sufficient confidence that the individual has gout, into a Phase 3 randomized clinical trial of a new urate-lowering agent with unclear efficacy and safety. The score at which the majority considered an individual as having gout or not fell at the same threshold as that identified as the cutoff score that maximized the sum of sensitivity and specificity.

Final criteria scoring. With face validity of the initial scoring system confirmed and a threshold identified, the raw relative weights of the domain categories and the threshold score were rescaled and rounded into whole numbers to make the scoring system as simple as possible, while retaining the relative weighting produced by the expert panel. The maximum possible score in the final criteria is 23. A threshold score of ≥8 classifies an individual as having gout.

A unique aspect of the new classification criteria is that there are 2 categories that elicit *negative* scores. Specifically, if the synovial fluid is MSU negative, *2 points are subtracted* from the total score. Similarly, if the serum urate level is <4 mg/dl (<0.24 mmoles/liter), *4 points are subtracted* from the total score. This approach was taken to emphasize that these findings reduce the probability of gout. The lowest category in each domain has a score of 0 and is therefore not explicitly depicted in the final criteria table; however, for serum urate level, the category that receives a score of 0 is 4−<6 mg/dl (0.24−<0.36 mmoles/liter). If imaging is not performed, those categories are also scored as 0. The final criteria are presented in Table 2. A web-based calculator can be accessed at http://goutclassificationcalculator.auckland.ac.nz, as well as through the ACR and EULAR web sites.

Results of testing of the new gout classification criteria and comparison with existing published criteria. In the SUGAR validation data set (n = 330), the sensitivity of the new classification criteria was 0.92, and specificity was 0.89 (Table 3). The performance of the criteria was also tested using only clinical parameters, i.e., without MSU results, scored as 0 (unknown/not done) and without imaging (i.e., radiographic, ultrasound, or DECT imaging) results, scored as 0; this latter

scoring was in keeping with similar weighting being given to imaging studies that were negative versus not being performed in the discrete-choice experiments. In this setting, the sensitivity and specificity were 0.85 and 0.78.

When compared with existing published criteria (using their respective published thresholds), the new classification criteria performed well. For some existing criteria sets, presence of MSU crystals alone is sufficient to fulfill criteria; they are therefore 100% sensitive by definition. The new gout classification criteria also have MSU positivity as a sufficient criterion for classification, but the criteria set was not assessed in that regard, to avoid circularity. When the new classification criteria set was compared in its complete form (i.e., incorporating imaging and MSU data) with other published "full" criteria, some existing criteria had higher sensitivity, but all had lower specificity (Table 3). Additionally, for the clinical-parameters-only version of the new criteria, the sensitivity was better than that of all but 1 of the other clinical-only criteria sets, and the specificity was similar or better. The new gout classification criteria therefore performed well in both the "full" form and the "clinical-only" form.

Discussion

The new ACR/EULAR gout classification criteria represent an international collaborative effort that incorporates the latest published evidence on imaging modalities, a data-driven approach with MSU identification as a gold standard to reference key features, and a decision analytic approach to inform the weighting of the scoring system. This classification criteria set will enable a standardized approach to identifying a relatively homogeneous group of individuals who have the clinical entity of gout for enrollment into studies. The criteria permit characterization of an individual as having gout regardless of whether he or she is currently experiencing an acute symptomatic episode and regardless of any comorbidities. The new classification criteria have superior performance characteristics, with high sensitivity and improved specificity compared with previously published criteria. Arguably, specificity (leading to high positive predictive value) is of critical importance in most clinical studies since investigators need to have confidence that individuals who are enrolled in a study truly have the condition of interest.

Gout is unlike other rheumatic diseases in that a gold standard assessment is available, i.e., MSU crystal positivity. While this gold standard has high specificity, its feasibility and sensitivity may be inadequate, because of difficulty with aspiration of joints (particularly small ones) and/or examination of the sample under polarizing microscopy. Thus, although MSU crystal results are extremely helpful when positive, they are not a feasible universal standard, particularly because many potential study subjects are likely to be recruited from nonrheumatology settings. We aimed to develop a new set of criteria that could be flexible enough to enable accurate classification of gout regardless of MSU status; a clinical-only version can be considered for use in settings in which synovial fluid or tophus aspiration is not feasible. Nonetheless, in recognition of its gold standard status, the expert panel set the presence of MSU crystal positivity in a symptomatic joint or bursa as sufficient for classifying an individual as having gout. It should be recognized that classification criteria are not intended for use in making a diagnosis in a clinical setting (35). Thus, in clinical practice, joint or tophus aspiration remains an essential component of establishing a diagnosis of gout.

As with most diseases, there is a gradient of probability of truly having the disease based on signs and symptoms. The threshold chosen for this classification criteria set yielded the best combination of sensitivity and specificity. While for certain purposes a higher sensitivity (lower score) may be preferable (e.g., general population survey to determine the public health burden of gout for resource planning), a higher specificity (higher score) may be desirable for others (e.g., genetic association studies in which accurate phenotyping is critical). Furthermore, classification criteria are not intended to characterize the severity of disease, but only its presence. Additionally, classification criteria should be applied only to the intended population—those who meet the entry criteria. Performance characteristics of any classification criteria set will necessarily be altered if the criteria are applied to those other than the intended population.

A limitation of our current effort is that there is still a relative paucity of data and of clinical experience to fully test advanced imaging data empirically. As more studies are published, there may be additional imaging signs and/or modalities found to have sufficient specificity for gout that could be incorporated into future criteria. We also realized that some investigators may not have access to imaging and therefore aimed to develop criteria that would still perform well in the absence of imaging data. In the discrete-choice experiments, the lack of imaging data was weighted the same as for studies performed with negative results, supporting the validity of using the scoring system in the absence of imaging data. We did not address asymptomatic hyperuricemia, since the purpose of classification criteria is to identify individuals with a clinical entity for clinical stud-

ies. There is certainly an interest in studying asymptomatic hyperuricemia, but this was beyond the scope of the current activity; the expert panel agreed that its charge was to classify individuals with symptomatic disease as evidence of a clinical condition. The present criteria set represents an attempt to optimize both sensitivity and specificity for enrollment into trials and prospective epidemiologic studies. Further testing of the criteria in additional samples, particularly in settings from which individuals with gout are likely to be recruited (e.g., primary care), and other study types, is warranted.

This study provides a number of insights relating to the likelihood of gout. First, the clinical picture of gout as an episodic disease with stereotypical features and a predilection for lower-extremity joints, particularly the first metatarsophalangeal joint, was captured in the SUGAR study, despite concerns that the study design might lead to selection bias. Second, there were certain conditions that strongly reduced the likelihood of gout: synovial fluid from a symptomatic joint or bursa that was negative for MSU crystals, and a serum urate level of $<$4 mg/dl (0.24 mmoles/liter). While such findings would not necessarily rule out gout, they were weighted in the discrete-choice experiments such that they lower the probability of gout. Third, both the SUGAR subjects and the paper patient cases were derived from a large international pool, supporting generalizability of these criteria. Finally, advanced imaging modalities have been incorporated into classification criteria for gout for the first time.

In summary, the 2015 ACR/EULAR classification criteria for gout represent an advance over previous criteria, with improved performance characteristics and incorporation of newer imaging modalities. These criteria may be considered as inclusion criteria for future studies of clinical gout.

ACKNOWLEDGMENTS

We are grateful to the following investigators for contributing additional paper patient cases: Drs. Everardo Alvarez Hernandez, Ruben Burgos, Geraldo Castelar, Marco Cimmino, Tony Dowell, Angelo Gaffo, Rebecca Grainger, Leslie Harrold, Phillip Helliwell, Changtsai Lin, Worawit Louthrenoo, Claudia Schainberg, Naomi Schlesinger, Carlos Scire, Ole Slot, Lisa Stamp, Robert Terkeltaub, Harald Vonkeman, Zeng Xuejun. We would like to thank Dr. Thomas Bardin for participating in ranking of the paper cases. We would like to acknowledge and thank Dr. Esperanza Naredo for her advice regarding standardization of the ultrasound definition of double-contour sign. We are also grateful to the following additional investigators who collected data for the SUGAR study: Drs. Lorenzo Cavagna, Jiunn-Horng Chen, Yi-Hsing Chen, Yin-Yi Chou, Hang-Korng Ea, Maxim Eliseev, Martijn Gerritsen, Matthijs Janssen, Juris Lazovskis, Geraldine McCarthy, Francisca Sivera, Ana Beatriz Vargas-Santos, Till Uhlig, Douglas White, and all of the authors of the SUGAR study (full list in ref. 21). We would like to acknowledge and thank Ian Sayer (Application Specialist, Information Services, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand) for his work on developing the gout classification calculator web page.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Neogi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Neogi, Jansen, Dalbeth, Fransen, Schumacher, Taylor.

Acquisition of data. Neogi, Jansen, Dalbeth, Fransen, Schumacher, Berendsen, Brown, Choi, Edwards, Janssen, Lioté, Naden, Nuki, Ogdie, Perez-Ruiz, Saag, Singh, Sundy, Tausche, Vaques-Mellado, Yarows, Taylor.

Analysis and interpretation of data. Neogi, Jansen, Dalbeth, Fransen, Schumacher, Berendsen, Brown, Choi, Edwards, Janssen, Lioté, Naden, Nuki, Ogdie, Perez-Ruiz, Saag, Singh, Sundy, Tausche, Vaques-Mellado, Yarows, Taylor.

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Arthritis Care & Research
Vol. 64, No. 10, October 2012, pp 1431–1446
DOI 10.1002/acr.21772
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SPECIAL ARTICLE

2012 American College of Rheumatology Guidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia

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Introduction

Gout is a disorder that manifests as a spectrum of clinical and pathologic features built on a foundation of an excess body burden of uric acid, manifested in part by hyperuricemia, which is variably defined as a serum urate level greater than either 6.8 or 7.0 mg/dl (1,2). Tissue deposition of monosodium urate monohydrate crystals in supersaturated extracellular fluids of the joint, and certain other

Supported by a research grant from the American College of Rheumatology and by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant K24-AR-063120).

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Significance & Innovations

- Patient education on diet, lifestyle, treatment objectives, and management of comorbidities is a recommended core therapeutic measure in gout.
- Xanthine oxidase inhibitor (XOI) therapy with either allopurinol or febuxostat is recommended as the first-line pharmacologic urate-lowering therapy (ULT) approach in gout.
- Serum urate level should be lowered sufficiently to durably improve signs and symptoms of gout, with the target <6 mg/dl at a minimum, and often <5 mg/dl.
- The starting dosage of allopurinol should be no greater than 100 mg/day and less than that in moderate to severe chronic kidney disease (CKD), followed by gradual upward titration of the maintenance dose, which can exceed 300 mg daily even in patients with CKD.
- Prior to initiation of allopurinol, rapid polymerase chain reaction–based HLA–B*5801 screening should be considered as a risk management component in subpopulations where both the HLA–B*5801 allele frequency is elevated and the HLA–B*5801–positive subjects have a very high hazard ratio ("high risk") for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse CKD and all those of Han Chinese and Thai descent).
- Combination oral ULT with 1 XOI agent and 1 uricosuric agent is appropriate when the serum urate target has not been met by appropriate dosing of an XOI.
- Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULT options.

sites, mediates most of the clinical and pathologic features of gout. Typically, the disease initially presents as acute episodic arthritis. Gout also can manifest as chronic arthritis of 1 or more joints (1,2). Tophi, mainly found in articular, periarticular, bursal, bone, auricular, and cutaneous tissues, are a pathognomonic feature of gout, and are detectable by physical examination and/or by imaging approaches and pathology examination (3–5). Renal manifestations of gout include urolithiasis, typically occurring with an acidic urine pH (1,2). Chronic interstitial nephropathy, mediated by monosodium urate monohydrate crystal deposition in the renal medulla, can occur in severe disease, but is currently considered to be an uncommon clinical manifestation of gout.

Gout is one of the most common rheumatic diseases of adulthood, with a self-reported prevalence in the US recently estimated at 3.9% of adults (~8.3 million people) (6). The prevalence of gout has risen in many countries (e.g., New Zealand) and especially in the US over the last few decades, mediated by factors such as an increased prevalence of comorbidities that promote hyperuricemia, including hypertension, obesity, metabolic syndrome, type 2 diabetes mellitus, and chronic kidney disease (CKD) (7–10). Other factors in the rising prevalence of gout include certain dietary trends and widespread prescriptions of thiazide and loop diuretics for cardiovascular diseases (11). Many gout patients, including the growing subset of elderly patients affected with gout, have complex comorbidities and medication profiles that complicate overall management (12). Long-term morbidity and impairment of

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Dr. Dinesh Khanna has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Novartis and Ardea and (more than $10,000 each) from Takeda and Savient, and has served as a paid investment consultant for Guidepoint. Dr. Puja P. Khanna has received speaking fees (less than $10,000) from Novartis and (more than $10,000) from Takeda, and has served on the advisory board for Novartis. Dr. Pillinger has received speaking fees and/or honoraria (less than $10,000 each) from the RA Investigator Network, NY Downtown Hospital, Winthrop Hospital, and Einstein College of Medicine. Dr. Perez-Ruiz has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Novartis, Menarini, and Savient, and (more than $10,000) from Ardea. Dr. Lioté has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Novartis Global, Novartis France, and Ipsen, and has served as a paid investment consultant for Gerson Lehrman Group. Dr. Choi has served on the advisory boards (less than $10,000 each) for Takeda, URL, and Savient. Dr. Singh has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Ardea, Savient, Allergan, and Novartis, and (more than $10,000) from Takeda, and has received investigator-initiated grants from Takeda and Savient. Dr. Dalbeth has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Takeda, Ardea, and Novartis, has received research funding from Fonterra, and holds a patent from Fonterra for milk products for gout. Dr. Niyyar has received honoraria (less than $10,000) from the American Society of Nephrology. Dr. Kerr has served as a study investigator (more than $10,000 each) for Savient and Nuon. Dr. Edwards has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Savient, Takeda, Ardea, and Regeneron, and (more than $10,000) from Novartis, and has given expert testimony for Novartis. Dr. Mandell has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Savient, Novartis, and Pfizer. Dr. Schumacher has received consultant fees (less than $10,000 each) from Pfizer, Regeneron, West-Ward, and Ardea, and (more than $10,000) from Novartis. Dr. Terkeltaub has received consultant fees (less than $10,000 each) from Takeda, Savient, Ardea, BioCryst, URL, Regeneron, Pfizer, Metabolex, Nuon, Chugai, EnzymeRx, Ajanta, Anadys, Celgene, Isis, and Prescription Solutions, and (more than $10,000) from Novartis, has received grant support from the VA San Diego Healthcare System and the NIH, and has served as a paid investment consultant for Leerink Swann, Medacorp, and Guidepoint.

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Submitted for publication January 9, 2012; accepted in revised form June 15, 2012.

health-related quality of life are now better appreciated in many gout patients, particularly those with multiple comorbidities and/or chronic gouty arthritis (13,14). Despite advanced understanding of the molecular bases of hyperuricemia and gouty inflammation and the extensive practice experience of many providers, substantial quality of care gaps exist in gout management (15). Moreover, significant shortfalls in patient education and adherence have been identified in gout (16).

On behalf of the American College of Rheumatology (ACR), we were charged with developing systematic nonpharmacologic and pharmacologic recommendations for effective treatments in gout with an acceptable risk/benefit ratio. Our assignment was to focus on 4 specific domains in gout management. Two of these domains are addressed herein, i.e., urate-lowering therapy (ULT) and chronic gouty arthritis with tophaceous disease detected on physical examination (designated by the ACR with the terminology "chronic tophaceous gouty arthropathy" [CTGA] and specifically represented in the fundamental case scenarios 7–9 described herein). The remaining 2 domains (analgesic and antiinflammatory management of acute gouty arthritis and pharmacologic antiinflammatory prophylaxis of attacks of gouty arthritis) are addressed in part 2 of the guidelines as a separate article (17).

There are multiple lines of epidemiologic and experimental evidence that hyperuricemia, via the effects of excess soluble urate, may play a role in some human renal, cardiovascular, and metabolic comorbidities also frequently associated with gout (7–10). We did not address pharmacologic management of asymptomatic hyperuricemia due to a paucity of prospective, randomized, controlled human research trials in that area (18).

We were charged by the ACR with developing gout recommendations based on evidence as available, at an international level, for rheumatologists and other health care providers, including other subspecialists, primary care practitioners, nurse practitioners, physician assistants, and allied health professionals. The ACR requested that we apply the established RAND/University of California at Los Angeles (UCLA) Appropriateness Method (19) to generate recommendations, and we engaged a diverse international panel of experts. Creating a novel classification of gout as a disease, new gout diagnostic criteria, or a definition of treatment outcomes was beyond the scope of this work. Instead, we generated multifaceted case scenarios to elucidate decision making based primarily on clinical and laboratory test–based data that can be obtained on a gout patient in an office practice setting.

Guidelines for gout management have been generated in the last decade, at the national or multinational society level and independent of industry sponsorship, by the European League Against Rheumatism (EULAR) (20,21), the Dutch College of General Practitioners (22), the Japanese Society of Gout and Nucleic Acid Metabolism (23), and the British Society for Rheumatology (BSR) (24). Moreover, the National Institute for Health and Clinical Excellence single technology appraisal process has been applied to ULT in gout patients receiving febuxostat (25). New guidelines were requested by the ACR, since the understanding of gout risk factors has been greatly augmented by recent clinical research (12). Moreover, ULT options recently increased via clinical development and drug regulatory agency approval of new pharmacologic agents (febuxostat and the biologic drug pegloticase) (26,27). New imaging approaches for gout that can detect radiographic changes of early disease not visualized by plain radiography (e.g., high-resolution ultrasound, dual-energy computed tomography [CT]) (28,29) are being investigated for impact on gout diagnosis, assessment of disease burden and severity, and choices and effectiveness of management. Developments such as these are considered in the work of this committee, which was built on several key assumptions (Table 1).

Table 1. Key assumptions in the process applied to develop the recommendations

1. Recommendations were developed using the RAND/University of California at Los Angeles methodology, which assesses level of evidence and safety and quality, but does not take comparisons of cost and cost-effectiveness of therapies into consideration.
2. The guidelines focused on clinically-based decision making in common scenarios and not on rare case presentations.
3. Multiple scenarios were developed for acute treatment and chronic gout for voting purposes and are NOT meant to be disease classification criteria for gout.
4. The project did not list specific drug choices, contraindications, and dosing in the presence of comorbidities associated with gout or with potential drug–drug interaction. These decisions are left with the practitioner, based on evaluation of the risk/benefit ratio when prescribing each therapy, the drug dosing and safety labeling, and other widely available databases and accessible sources of general medical information about potential drug-related adverse events.
5. When a particular drug is not recommended, it does not imply that it is contraindicated. Similarly, if a hierarchy or sequence of a treatment is recommended, it does not necessarily imply that an agent lower in the hierarchy is contraindicated.
6. It is assumed that the diagnosis of gout was correct before initiation of any management option.
7. It is not always possible for the task force panel to reach a consensus on a case scenario (see Supplemental Figure 3 for examples of voting scenarios, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

The ACR gout guidelines are designed to emphasize safety and quality of therapy and to reflect best practice, as evaluated by a diverse group of experts that examined the level of evidence available at the time. Importantly, societal cost of health care and cost and cost-effectiveness differences between therapies are excluded from analysis by the RAND/UCLA Appropriateness Method (19) (Table 1). Individual results of this work are designated as "recommendations" rather than guidelines, in order to reflect the nonprescriptive nature of decision making evaluated by experts and based on available evidence at the time. The recommendations cannot substitute for individual-

ized direct assessment of the patient, coupled with clinical decision making by a competent health care practitioner. Treatment recommendations also assume appropriate attention to potential drug interactions (e.g., with anticoagulants, azathioprine, amoxicillin) and effects of comorbidities such as diabetes mellitus and renal, cardiac, gastrointestinal, and hepatic disease (Table 1). The motivation, financial circumstances, and preferences of the gout patient play a very important role. Moreover, the recommendations for gout management presented here are not intended to limit or deny third party payor coverage of health care costs for groups or individual patients with gout.

Materials and methods

Project design, development of recommendations, and grading of evidence. The overall design of the project is schematized in Supplemental Figure 1 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). The RAND/UCLA consensus methodology, developed in the 1980s, incorporates both Delphi and nominal group methods (19,30), and was successfully used to develop other guidelines commissioned by the ACR. The purpose of this methodology is to reach a consensus among experts, with an understanding that published literature may not be adequate to provide sufficient evidence for day-to-day clinical decision making. The RAND/UCLA method requires 2 groups of experts: a core expert panel (CEP) that provides input into case scenario development and preparation of a scientific evidence report, and a task force panel (TFP) that votes on these case scenarios. Our CEP consisted of leaders for each domain (see Supplemental Figure 2, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Pharmacologic approaches and diet, lifestyle, and nonpharmacologic measures (e.g., weight loss, exercise) were addressed within each domain. The CEP leaders communicated with an international panel of gout experts and the principal investigators (PIs; JDF, PPK, DK, RT) to develop initial case scenarios that reflect broad differences in severity of the disease and its clinical manifestations. In addition, there were weekly interactive teleconferences between the domain leaders and PIs to refine case scenarios. Although a previous systematic review for gout has been performed by EULAR, as a prime example, we performed our own systematic review of pertinent literature. The resultant scientific evidence report was given to the TFP in conjunction with clinical scenarios representing differing degrees of disease activity. There were multiple questions of interest and alternative options presented for each case scenario.

By ACR mandate, the TFP had a majority of members without a perceived potential conflict of interest (COI), and had diverse experience and expertise, as described in detail in Supplemental Figure 2 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). The TFP included 7 rheumatologists (including 1 Chair of Internal Medicine and 1 Internal Medicine Residency Training Program Director), 2 primary care physicians, a nephrologist, and a patient representative. There were 2 rounds of ratings, the first anonymous, with the members of the TFP instructed to rank each of the potential elements of the guidelines on a risk/benefit basis ranging from 1–9 on a Likert scale using the Delphi process, followed by a face-to-face group discussion and then revoting of the same scenarios. A vote of 1–3 on the Likert scale was rated as *inappropriate* (risks clearly outweigh the benefits), a vote of 4–6 was considered *uncertain* (risk/benefit ratio is uncertain), and a vote of 7–9 was rated as *appropriate* (benefits clearly outweigh the risks). Samples of votes taken and results are provided in Supplemental Figure 3 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Votes on case scenarios were translated into recommendations if the median voting score was graded 7–9 (appropriate) and if there was no significant disagreement, defined as no more than 1 of 3 of the votes graded as inappropriate for the scenario. The final rating was done anonymously in a 2-day face-to-face meeting, facilitated by an experienced moderator (NW). During the face-to-face TFP meeting, some case scenarios were clarified for content or verbiage and revoted on by the TFP.

The level of evidence supporting each recommendation was ranked based on previous methods used by the American College of Cardiology (31) and applied to recent ACR recommendations (32,33). Level A grading was assigned to recommendations supported by multiple (i.e., >1) randomized clinical trials or meta-analyses. Level B grading was assigned to the recommendations derived from a single randomized trial or nonrandomized studies. Level C grading was assigned to consensus opinion of experts, case studies, or standard of care.

Systematic review. PubMed and the Cochrane Central Register of Controlled Trials from the 1950s to the present were searched to find articles on gout with the help of an experienced librarian. We used a search strategy based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials. The search was expanded to include articles discussing research designs such as cohort, case–control, and cross-sectional studies. Limits included English language and the exclusion of "animal only" studies. The exact terms, process, and results of the search are summarized in Supplemental Figure 4 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Clinical case descriptions. The TFP evaluated clinical scenarios with differences in frequency of acute gout symptoms and differences related to the presence or extent of chronic findings (tophi, synovitis) on physical examination, similar to what a clinician might see in a busy practice. Scenarios were divided into mild, moderate, and severe disease activity in each of 3 distinct "treatment groups" (Figures 1A and B). In generating these 9 fundamental clinical case scenarios, mild disease activity levels in each treatment group were meant to represent patients at the lowest disease activity level for which most clinicians would consider initiating or altering a specific med-

GOUT CASE SCENARIOS

Symptoms	Tophus or Tophi detected on Physical Exam	Frequency	CASE SCENARIO NUMBER
Intermittent symptoms	NO	Infrequent Symptoms (≤ 1 attack/yr)	*1*
	NO	Frequent Symptoms (2-6 attacks/yr)	*2*
	NO	Very Frequent Symptoms (> 7 attacks/yr)	*3*
Intermittent symptoms	YES	Infrequent Symptoms (≤ 1 attack/yr)	*4*
	YES	Frequent Symptoms (2-6 attacks/yr)	*5*
	YES	Very Frequent Symptoms (> 7 attacks/yr)	*6*

A

Case scenarios for Chronic Tophaceous Gouty Arthropathy

Disease Severity	Characteristics	CASE SCENARIO NUMBER
Mild	•Simple chronic tophaceous gouty arthropathy •Affecting 1 joint •Stable disease	*7*
Moderate	•Simple chronic tophaceous gouty arthropathy •Affecting 2-4 joints •Stable disease	*8*
Severe	•Chronic tophaceous gouty arthropathy of >4 joints OR • ≥1 unstable, complicated, severe articular tophus or tophi	*9*

B

Figure 1. Fundamental case scenarios evaluated by the task force panel (TFP). The TFP evaluated a broad spectrum of severity of gout, with presenting clinical information comparable to that encountered in practice. Scenarios were formulated iteratively by the core expert panel, as described in the text, and were not intended to serve as disease classification criteria. All case scenarios assumed that the diagnosis of gout was correct, and that there was some evidence of gout disease activity. Three distinct "treatment groups" for these recommendations, each with 3 case scenarios designed to succinctly represent clinically-based decision making and totaling 9 in all, are shown. The treatment group with intermittent attacks of acute gout but no tophi detected on physical examination was subdivided based on increasing yearly frequency of episodes of acute gouty arthritis of at least moderate to severe pain intensity (case scenarios 1–3; **A**). Gout associated with clinically apparent high body urate burden was evaluated in case scenarios where there were ≥1 tophi on physical examination, and either **A,** intermittently symptomatic acute gouty arthritis (case scenarios 4–6), or **B**, chronic joint symptoms due to synovitis attributable to gout or articular tophus or tophi in case scenarios 7–9 (the domain termed chronic tophaceous gouty arthropathy [CTGA]). Severity of case scenarios in the CTGA domain was distinguished by extent and characteristics of the tophi and chronic arthropathy, with variable inflammatory and deforming features detected on physical examination (see Figure 2).

ication regimen. Conversely, the severe disease activity level was intended to represent patients with disease activity greater than or equal to that of the "average" subject studied in a clinical trial. The case scenarios were not intended to serve as classification criteria. To allow the TFP to focus on management decisions, each case scenario had the assumption that the diagnosis of gout was correct. In addition, it was assumed that there was some clinical evidence of gout disease activity. This included intermittent symptoms of variable frequency, specifically presented to the TFP as episodes of acute gouty arthritis of at least moderate to severe pain intensity (17). Other clinical evidence of gout disease activity, presented to the TFP in specific case scenarios, was tophi detected by physical examination, or alternatively, chronic symptomatic arthritis (i.e., "chronic arthropathy" or "synovitis") due to gout, with or without confirmed joint damage (e.g., deformity, erosion due to gout on an imaging study) (Figure 2). Hyperuricemia was defined here as a serum urate level >6.8 mg/dl (2). We determined all aspects of case scenario definitions by a structured iterative process, using regular e-mail and teleconferences at least once per month. Multiple revisions to the proposed parameters were carried out, until accepted by the CEP domain leaders.

Definitions of pharmacologic therapeutic agents. Medication classes evaluated in the case scenarios were defined as follows: xanthine oxidase inhibitor (XOI) refers to allopurinol or febuxostat, and uricosuric agents were defined to include agents available in the US (probenecid and off-label use [as uricosuric therapy] of fenofibrate and losartan), but did not include sulfinpyrazone or benzbromarone. Other agents and modalities were self-explanatory. Evaluation by the TFP of effectiveness of a given therapeutic option assumed that patients in the case scenarios received the maximum tolerated typical dose for a period of time sufficient to accurately assess therapeutic response, unless otherwise indicated.

Managing perceived potential COI. Perceived potential COI was managed in a prospective and structured manner. Specifically, all participants intellectually involved in the project, whether authors or not, were required to fully and prospectively disclose relationships with pharmaceutical companies with a material interest in gout (see Supplemental Figure 2 and Appendix A, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Disclosures were updated every 6 months, and for the PIs, CEP, and TFP, updated just prior to the face-to-face meeting. A summary listing of all perceived potential COI was disseminated to all participants in the project, and is available in Supplemental Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Based on the policies of the ACR, which are aligned with those of many medical societies, no more than 49% of the project participants could have a COI at any given time. It was required that the project PI (JDF) remain without perceived potential COI prior to and during the process.

Results

Primary principles of management for all gout case scenarios. The TFP generated recommendations for a systematic nonpharmacologic and pharmacologic management approach intended to be applicable to all patients with gout, which is summarized in Figure 3. This was based on the assumption that the diagnosis of gout was correct before initiation of management. The approach highlighted patient education on the disease and treat-

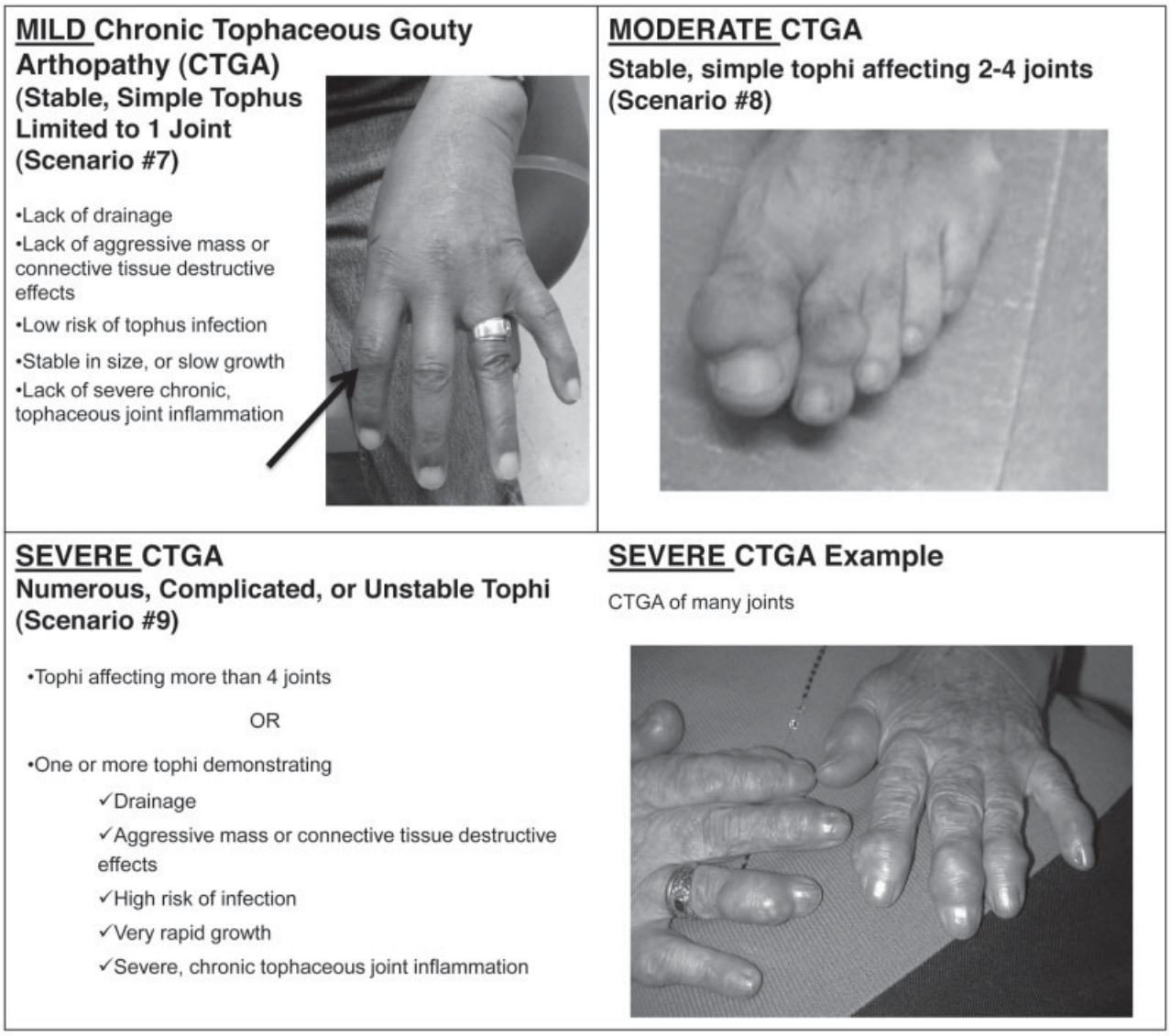
MILD Chronic Tophaceous Gouty Arthopathy (CTGA)
(Stable, Simple Tophus Limited to 1 Joint
(Scenario #7)
•Lack of drainage
•Lack of aggressive mass or connective tissue destructive effects
•Low risk of tophus infection
•Stable in size, or slow growth
•Lack of severe chronic, tophaceous joint inflammation
MODERATE CTGA
Stable, simple tophi affecting 2-4 joints
(Scenario #8)
SEVERE CTGA
Numerous, Complicated, or Unstable Tophi
(Scenario #9)
•Tophi affecting more than 4 joints
OR
•One or more tophi demonstrating
✓Drainage
✓Aggressive mass or connective tissue destructive effects
✓High risk of infection
✓Very rapid growth
✓Severe, chronic tophaceous joint inflammation
SEVERE CTGA Example
CTGA of many joints

Figure 2. Detailed pictorial representations of chronic arthropathy in chronic tophaceous gouty arthropathy (CTGA) case scenarios presented to the task force panel (TFP). A core element of our approach was to present the TFP and the readership with specifically detailed summaries of the CTGA case scenarios (case scenarios 7–9 in Figure 1B), including pictorial examples, to allow focus on clinical information that prompts management decisions. The photograph on the top left was provided by Dr. Robert Terkeltaub; the photographs on the top and bottom right were provided by Dr. Fernando Perez-Ruiz.

ments and their objectives, and initiation of diet and lifestyle recommendations, including the particular role of uric acid excess in gout and as the key long-term treatment target (evidence B) (34). The TFP also recommended, on a case-by-case basis, careful consideration of potential elimination of serum urate–elevating prescription medications that might be nonessential for the optimal management of comorbidities (e.g., hypertension, hyperlipidemia, or major organ transplant) in a given patient. Prime examples of urate-elevating medications are thiazide and loop diuretics, niacin, and calcineurin inhibitors (evidence C). However, the TFP, without a specific vote, recognized the particular benefits of thiazides for blood pressure control and outcomes in many patients with hypertension. Although low-dose acetylsalicylic acid (aspirin ≤325 mg daily) elevates serum urate, the TFP did not recommend discontinuation of this modality as cardiovascular disease prophylaxis in gout patients. In discussion, without a specific vote, the TFP viewed the relative risks specifically attributable to the modest effects of low-dose aspirin on serum urate as negligible in gout management.

The TFP recommended that clinicians consider causes of hyperuricemia for all gout patients, and recommended a specific comorbidity checklist (evidence C) (Table 2). In doing so, the TFP specially recommended consideration, and if indicated, medical evaluation of certain agents and disorders that cause uric acid underexcretion or overproduction, which thereby could merit laboratory investigations such as urinalysis, renal ultrasound, a complete blood cell count with differential cell count, or urine uric acid quantification, as indicated. In this context, the TFP specifically recommended screening for uric acid overpro-

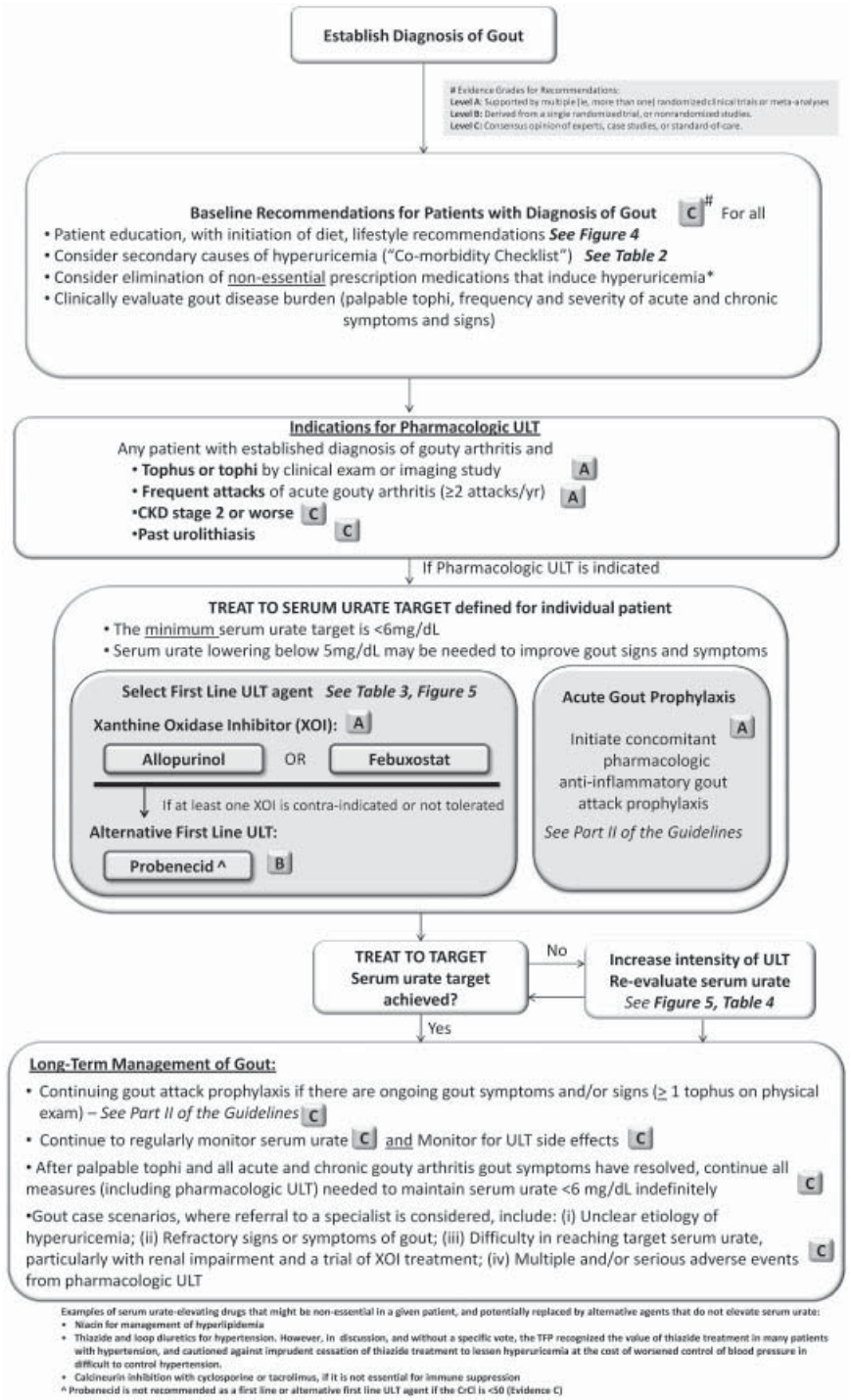
Establish Diagnosis of Gout
Evidence Grades for Recommendations:
Level A: Supported by multiple (ie, more than one) randomized clinical trials or meta-analyses
Level B: Derived from a single randomized trial, or nonrandomized studies.
Level C: Consensus opinion of experts, case studies, or standard-of-care.
Baseline Recommendations for Patients with Diagnosis of Gout C# For all
• Patient education, with initiation of diet, lifestyle recommendations See Figure 4
• Consider secondary causes of hyperuricemia ("Co-morbidity Checklist") See Table 2
• Consider elimination of non-essential prescription medications that induce hyperuricemia*
• Clinically evaluate gout disease burden (palpable tophi, frequency and severity of acute and chronic symptoms and signs)
Indications for Pharmacologic ULT
Any patient with established diagnosis of gouty arthritis and
• Tophus or tophi by clinical exam or imaging study A
• Frequent attacks of acute gouty arthritis (≥2 attacks/yr) A
•CKD stage 2 or worse C
•Past urolithiasis C
If Pharmacologic ULT is indicated
TREAT TO SERUM URATE TARGET defined for individual patient
• The minimum serum urate target is <6mg/dL
• Serum urate lowering below 5mg/dL may be needed to improve gout signs and symptoms
Select First Line ULT agent See Table 3, Figure 5
Xanthine Oxidase Inhibitor (XOI): A
Allopurinol OR Febuxostat
If at least one XOI is contra-indicated or not tolerated
Alternative First Line ULT:
Probenecid ^ B
Acute Gout Prophylaxis
A
Initiate concomitant pharmacologic anti-inflammatory gout attack prophylaxis
See Part II of the Guidelines
TREAT TO TARGET Serum urate target achieved?
No
Increase intensity of ULT Re-evaluate serum urate See Figure 5, Table 4
Yes
Long-Term Management of Gout:
• Continuing gout attack prophylaxis if there are ongoing gout symptoms and/or signs (≥ 1 tophus on physical exam) – See Part II of the Guidelines C
• Continue to regularly monitor serum urate C and Monitor for ULT side effects C
• After palpable tophi and all acute and chronic gouty arthritis gout symptoms have resolved, continue all measures (including pharmacologic ULT) needed to maintain serum urate <6 mg/dL indefinitely C
•Gout case scenarios, where referral to a specialist is considered, include: (i) Unclear etiology of hyperuricemia; (ii) Refractory signs or symptoms of gout; (iii) Difficulty in reaching target serum urate, particularly with renal impairment and a trial of XOI treatment; (iv) Multiple and/or serious adverse events from pharmacologic ULT C
Examples of serum urate-elevating drugs that might be non-essential in a given patient, and potentially replaced by alternative agents that do not elevate serum urate:
• Niacin for management of hyperlipidemia
• Thiazide and loop diuretics for hypertension. However, in discussion, and without a specific vote, the TFP recognized the value of thiazide treatment in many patients with hypertension, and cautioned against imprudent cessation of thiazide treatment to lessen hyperuricemia at the cost of worsened control of blood pressure in difficult to control hypertension.
• Calcineurin inhibition with cyclosporine or tacrolimus, if it is not essential for immune suppression
^ Probenecid is not recommended as a first line or alternative first line ULT agent if the CrCl is <50 (Evidence C)

Figure 3. Baseline recommendations and overall strategic plan for patients with gout. This algorithm summarizes overall treatment strategies and flow of management decisions for gout. Certain elements, including nonpharmacologic and pharmacologic measures, the approach to refractory disease, and treatment and antiinflammatory prophylaxis of acute gout attacks, are developed further in Tables 2–4 and Figures 4 and 5, and in part 2 of the guidelines, as referenced in the figure. Evidence grades (A–C, as indicated) are summarized for each task force panel (TFP) recommendation, and the text discusses in detail each aspect of clinical decision making. ULT = urate-lowering therapy; CKD = chronic kidney disease; CrCl = creatinine clearance.

Table 2. Specific recommendation of a comorbidity checklist for gout patients

Appropriate to consider in the clinical evaluation, and if clinically indicated, to evaluate (evidence C for all)*
Obesity, dietary factors
Excessive alcohol intake
Metabolic syndrome, type 2 diabetes mellitus
Hypertension†
Hyperlipidemia, modifiable risk factors for coronary artery disease or stroke
Serum urate–elevating medications†
History of urolithiasis
Chronic kidney, glomerular, or interstitial renal disease (e.g., analgesic nephropathy, polycystic kidney disease)
In selected cases, potential genetic or acquired cause of uric acid overproduction (e.g., inborn error of purine metabolism or psoriasis, myeloproliferative, or lymphoproliferative disease, respectively)
Lead intoxication

* Evidence grades for recommendations: level A = supported by multiple (i.e., >1) randomized clinical trials or meta-analyses; level B = derived from a single randomized trial or nonrandomized studies; level C = consensus opinion of experts, case studies, or standard of care.
† The task force panel, without a specific vote, recognized the particular benefits of thiazide diuretics for blood pressure control and outcomes in many patients with hypertension.

duction (by urine uric acid evaluation) in patient subsets with gout clinical disease onset before age 25 years (evidence C) or a history of urolithiasis (evidence C).

The TFP provided guidance for referral to a specialist, with caution to avoid appearing self-serving. Although limited by the absence of outcomes data on potential benefits of referral, the TFP recommended that gout case scenarios including any of the following should be among those where referral to a specialist is considered (evidence C for all): 1) unclear etiology of hyperuricemia; 2) refractory signs or symptoms of gout; 3) difficulty in reaching the target serum urate level, particularly with renal impairment and a trial of XOI treatment; and 4) multiple and/or serious adverse events from pharmacologic ULT.

Clinical evaluation of gout disease activity and burden. The TFP recommended clinical evaluation of gout disease symptom severity and burden in individual patients by history and a thorough physical examination for symptoms of arthritis and signs such as tophi and acute and chronic synovitis (evidence C). To be actionable by clinicians, the authors without a specific TFP vote suggested that clinicians can work with patients to record and estimate the number per year and severity (17) of acute attacks of gouty arthritis per year.

Core recommendations for nonpharmacologic ULT measures in gout. The TFP recommended certain diet and lifestyle measures for the majority of patients with gout (evidence B and C for individual measures) (Figure 4). Many of the diet and lifestyle measures were recommended for decreasing the risk and frequency of acute gout attacks (12) and lowering serum urate levels, but the primary emphasis of the TFP recommendations in Figure 4 was on diet and lifestyle choices for promotion and maintenance of ideal health and prevention and optimal management of life-threatening comorbidities in gout patients, including coronary artery disease (35,36) and obesity, metabolic syndrome, diabetes mellitus, hyperlipidemia, and hypertension.

Dietary recommendations were grouped into 3 simple qualitative categories, termed "avoid," "limit," or "encourage" (Figure 4). This approach, with rare exceptions (37,38), reflected a general lack of specific evidence from prospective, blinded, randomized clinical intervention trials that linked consumed quantities of individual dietary components to changes in either serum urate levels or gout outcomes. Notably, the replication of hazardous lifestyle risk factors in a conventional clinical research trial would potentially pose both design and ethical difficulties. As such, the TFP deliberated on evidence regarding the impact of exposures to alcohol or purine-rich foods in a short timeframe. The evidence sources were epidemiologic studies of hyperuricemia and incident gout, including long-term prospective analyses (39–42) and internet-based case-crossover studies of specific exposures (43,44). The TFP recommended that gout patients limit their consumption of purine-rich meat and seafood (evidence B) (44) as well as high fructose corn syrup–sweetened soft drinks and energy drinks (evidence C), and encouraged the consumption of low-fat or nonfat dairy products (evidence B) (43) (Figure 4). The TFP voted to encourage vegetable intake in gout patients (evidence C) (Figure 4), having considered evidence in healthy subjects for lowered serum urate levels and urine urolithiasis risk factors associated with dietary vegetable intake (43,45). However, there was no specific TFP vote on the question of avoidance of excess purine intake from food sources other than meat and seafood, such as vegetables and legumes, in gout patients (44). The TFP recommended reduced consumption of alcohol (particularly beer, but also wine and spirits) and avoidance of alcohol overuse in all gout patients (evidence B) (Figure 4). The TFP further recommended abstinence from alcohol consumption for gout patients during periods of active arthritis, especially with inadequate medical control of the disorder and in CTGA (evidence C) (46). Significantly, in discussion by the TFP, without a specific vote, the TFP recognized that diet and lifestyle measures alone provide therapeutically insufficient serum urate–lowering effects and/or gout attack prophylaxis for a large fraction of individuals with gout (12). For example, some clinical trials on diet and fitness have reported only an ~10–18% decrease in serum urate (43). In further discussion by the TFP, again without a specific vote, the TFP viewed this degree of serum urate level lowering as beneficial for all case scenarios, but insufficient to achieve an effective serum urate target in those with sustained hyperuricemia substantially above 7 mg/dl.

Core recommendations for pharmacologic ULT, including the serum urate target. Here, and with all other recommendations for drug therapy in parts 1 and 2 of the 2012 ACR guidelines for gout, the recommendations assumed a lack of contraindications, intolerance, serious adverse events, or drug–drug interactions for given agents.

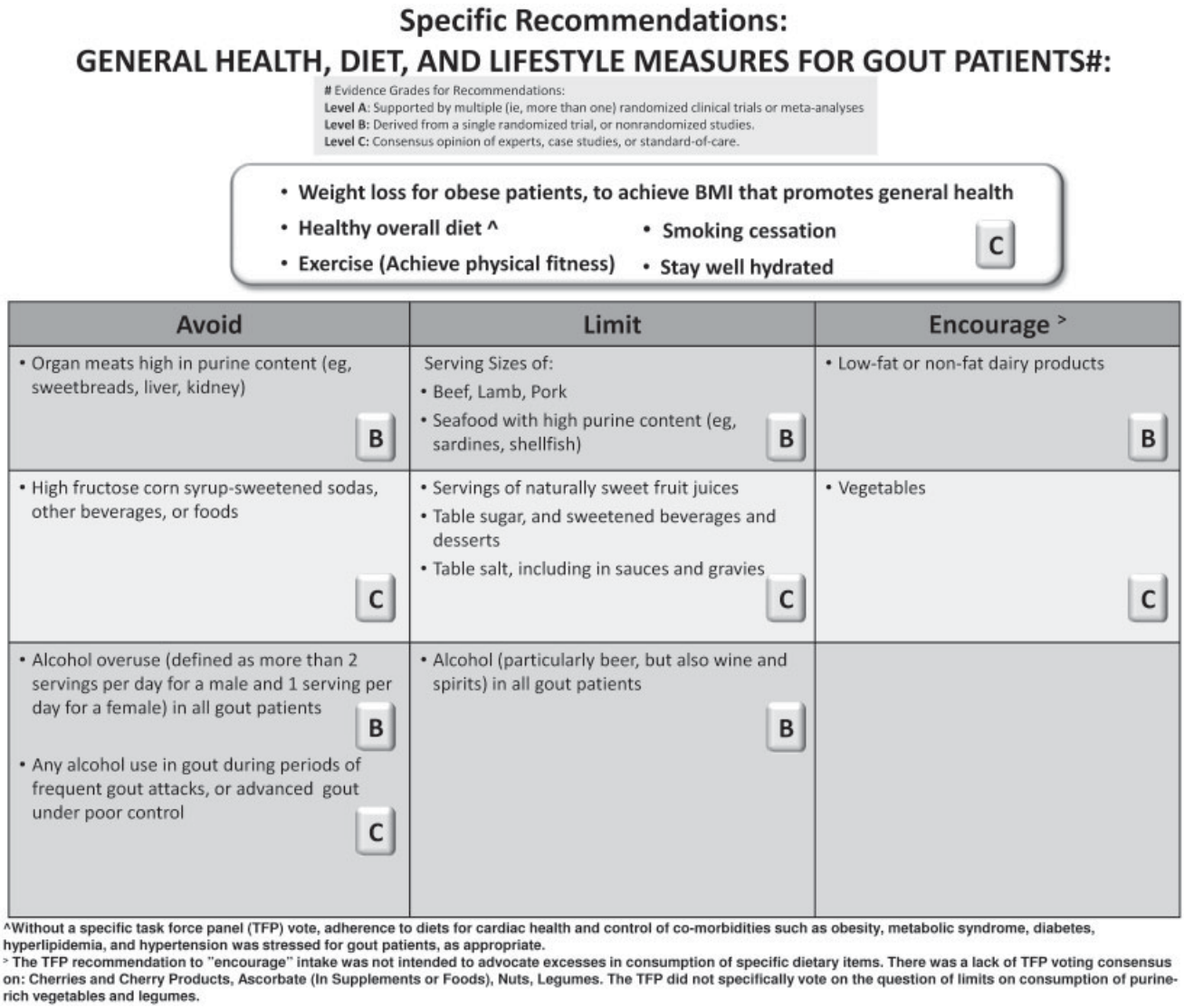
Specific Recommendations:
GENERAL HEALTH, DIET, AND LIFESTYLE MEASURES FOR GOUT PATIENTS#:
Evidence Grades for Recommendations:
Level A: Supported by multiple (ie, more than one) randomized clinical trials or meta-analyses
Level B: Derived from a single randomized trial, or nonrandomized studies.
Level C: Consensus opinion of experts, case studies, or standard-of-care.
• Weight loss for obese patients, to achieve BMI that promotes general health
• Healthy overall diet ^
• Exercise (Achieve physical fitness)
• Smoking cessation
• Stay well hydrated
C
Avoid
Limit
Encourage >
• Organ meats high in purine content (eg, sweetbreads, liver, kidney)
B
Serving Sizes of:
• Beef, Lamb, Pork
• Seafood with high purine content (eg, sardines, shellfish)
B
• Low-fat or non-fat dairy products
B
• High fructose corn syrup-sweetened sodas, other beverages, or foods
C
• Servings of naturally sweet fruit juices
• Table sugar, and sweetened beverages and desserts
• Table salt, including in sauces and gravies
C
• Vegetables
C
• Alcohol overuse (defined as more than 2 servings per day for a male and 1 serving per day for a female) in all gout patients
B
• Any alcohol use in gout during periods of frequent gout attacks, or advanced gout under poor control
C
• Alcohol (particularly beer, but also wine and spirits) in all gout patients
B
^Without a specific task force panel (TFP) vote, adherence to diets for cardiac health and control of co-morbidities such as obesity, metabolic syndrome, diabetes, hyperlipidemia, and hypertension was stressed for gout patients, as appropriate.
> The TFP recommendation to "encourage" intake was not intended to advocate excesses in consumption of specific dietary items. There was a lack of TFP voting consensus on: Cherries and Cherry Products, Ascorbate (In Supplements or Foods), Nuts, Legumes. The TFP did not specifically vote on the question of limits on consumption of purine-rich vegetables and legumes.

Figure 4. Specific task force panel (TFP) recommendations on general health, diet, and lifestyle measures for gout patients. The TFP recommendations on nonpharmacologic measures for gout patients are shown, including a program of broad diet and lifestyle measures. The recommendations encompass measures not only for decreasing the risk and frequency of acute gout attacks and lowering serum urate, but also with a major emphasis on maintenance of ideal health and prevention and best practice management of cardiovascular and metabolic diseases. Dietary recommendations were grouped into 3 simple qualitative categories, termed "avoid," "limit," and "encourage," reflecting a general lack of specific evidence from prospective, blinded, randomized clinical intervention trials linking consumed quantities of individual dietary components to changes in either serum urate or to gout signs and symptoms. Specific TFP votes on dietary components resulting in a "lack of consensus" are also cited. BMI = body mass index.

The TFP recommended gout with CKD stage 2–5 or end-stage renal disease as an appropriate indication, by itself, for pharmacologic ULT (evidence C) in patients with prior gout attacks and current hyperuricemia. In pharmacologic ULT, certain treatment choices (e.g., probenecid) and drug dosing decisions (e.g., allopurinol) are impacted by the creatinine clearance. The TFP, without a direct vote, discussed and recognized the clinical value of accurate measurement of creatinine clearance, not simply the serum creatinine, in ascertaining the degree of renal impairment. However, the scope of the project did allow for detailed prescriptive recommendations regarding specific ULT drug doses, usage of individual agents in the presence of a given degree of either renal impairment, or other comorbidities such as hepatic impairment.

TFP recommendations for pharmacologic ULT, shown graphically in Figure 3, included recommendation of XOI therapy with either allopurinol or febuxostat as the first-line pharmacologic approach (evidence A). The panel did not preferentially recommend either XOI over the other XOI drug. In doing so, the TFP weighed the lack of published safety data for febuxostat in the setting of stage 4 or worse CKD. Probenecid was recommended as an alternative first-line pharmacologic ULT option in the setting of contraindication or intolerance to at least 1 XOI agent (evidence B). However, the TFP did not recommend probenecid as a first-line ULT monotherapy in those with a creatinine clearance below 50 ml/minute.

The TFP recommended that pharmacologic ULT could be started during an acute gout attack, provided that effec-

tive antiinflammatory management has been instituted (evidence C). The TFP recommended regular monitoring of serum urate (every 2–5 weeks) during ULT titration, including continuing measurements once the serum urate target is achieved (every 6 months; evidence C). The TFP weighed this measure as particularly useful to monitor adherence, given that poor adherence to ULT is a common problem in gout patients (16).

The TFP recommended that the goal of ULT is to achieve a serum urate level target at a minimum of <6 mg/dl in all gout case scenarios (evidence A). Moreover, the TFP recommended that the target serum urate level should be lowered sufficiently to durably improve signs and symptoms of gout, including palpable and visible tophi detected by physical examination, and that this may involve therapeutic serum urate level lowering to below 5 mg/dl (evidence B).

Recommendations specific to allopurinol dosing and pharmacogenetics. TFP recommendations for use of allopurinol in gout are summarized in Table 3. Importantly, the TFP recommended that the starting dosage of allopurinol should be no greater than 100 mg per day (evidence B) (47), consistent with prior Food and Drug Administration (FDA) and EULAR guidelines (21). The rationale of the TFP was partly that a low allopurinol starting dose could reduce early gout flares after ULT initiation (26), and partly as a component of risk management with respect to the potential for severe hypersensitivity reaction to allopurinol (47), discussed in further detail below. The TFP recommended gradual upward titration of the allopurinol maintenance dose every 2–5 weeks to an appropriate maximum dose for gout, in order to treat to the serum urate target appropriate for the individual patient (evidence C).

The TFP weighed robust evidence that allopurinol monotherapy at doses of 300 mg or less daily failed to achieve the serum urate level target of <6 mg/dl (26,46) or <5 mg/dl (48,49) in more than half of the subjects with gout. The TFP reviewed small studies in which the allopurinol dose was titrated above 300 mg daily in gout with overall success in achieving the serum urate target (49,50). Importantly, in doing so, the TFP also recommended that the maintenance dosage of allopurinol can be raised above 300 mg per day, even in those with renal impairment, provided there is adequate patient education and regular monitoring for drug hypersensitivity and other adverse events, such as pruritis, rash, and elevated hepatic transaminases, as well as attention to potential development of eosinophilia (evidence B).

The TFP next considered the issue of measures to reduce the incidence of severe allopurinol hypersensitivity reactions, here termed allopurinol hypersensitivity syndrome (AHS). TFP discussion recognized the potential for hospitalization and severe morbidity and the reported mortality rate of 20–25% in AHS (51,52). The estimated incidence of AHS is ~1:1,000 in the US, and its spectrum includes not only Stevens-Johnson syndrome and toxic epidermal necrolysis, but also systemic disease with a clinical constellation of features such as eosinophilia, vasculitis, rash, and major end-organ disease (53). Concurrent thiazide use and renal impairment have been implicated as risk factors for AHS (50,54,55). A widely employed risk management strategy has been a non–evidence-based algorithm for allopurinol maintenance dosing, calibrated to renal impairment (evidence C) (56); importantly, the TFP did not recommend this strategy.

In their evaluation of the allopurinol starting dose as a component of risk management strategy, the TFP first weighed evidence that the highest risk of severe allopurinol hypersensitivity reaction is in the first few months of therapy. A recent case–controlled retrospective analysis of AHS and allopurinol starting dose (47) further supported the aforementioned recommendation by the TFP of a starting dose of allopurinol of no more than 100 mg daily, and the TFP recommendation of an even lower starting dose of allopurinol (50 mg daily) in stage 4 or worse CKD (evidence B).

Table 3. Core recommendations in the use of allopurinol and uricosuric ULT in gout*

Allopurinol
Starting dosage should be no greater than 100 mg/day for any patient, and start at 50 mg/day in stage 4 or worse CKD (evidence B)
Gradually titrate maintenance dose upward every 2–5 weeks to appropriate maximum dose in order to treat to chosen SUA target (evidence C)
Dose can be raised above 300 mg daily, even with renal impairment, as long as it is accompanied by adequate patient education and monitoring for drug toxicity (e.g., pruritis, rash, elevated hepatic transaminases; evidence B)
Prior to initiation, consider HLA–B*5801 in selected patients, specifically in subpopulations at higher risk for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse CKD, and Han Chinese and Thai irrespective of renal function; evidence A)
Uricosuric therapy
Probenecid is the first choice among uricosuric agents for ULT monotherapy (evidence B)
In gout patients with a creatinine clearance <50 ml/minute, probenecid is not recommended as first-line ULT monotherapy (evidence C)
Use of agents other than probenecid with clinically significant uricosuric effects, such as fenofibrate and losartan, can be therapeutically useful as components of a comprehensive ULT strategy (evidence B)
History of urolithiasis contraindicates first-line uricosuric urate-lowering monotherapy (evidence C)
Urinary uric acid should be measured before initiation of uricosuric ULT (evidence C)
Elevated urine uric acid indicative of uric acid overproduction contraindicates uricosuric ULT (evidence C)
Continue to monitor urinary uric acid during uricosuric ULT (evidence C)
Consider urine alkalinization (e.g., with potassium citrate) with monitoring of urine pH, in addition to increased fluid intake, as a risk management strategy for urolithiasis (evidence C)

* ULT = urate-lowering therapy; CKD = chronic kidney disease; SUA = serum uric acid.

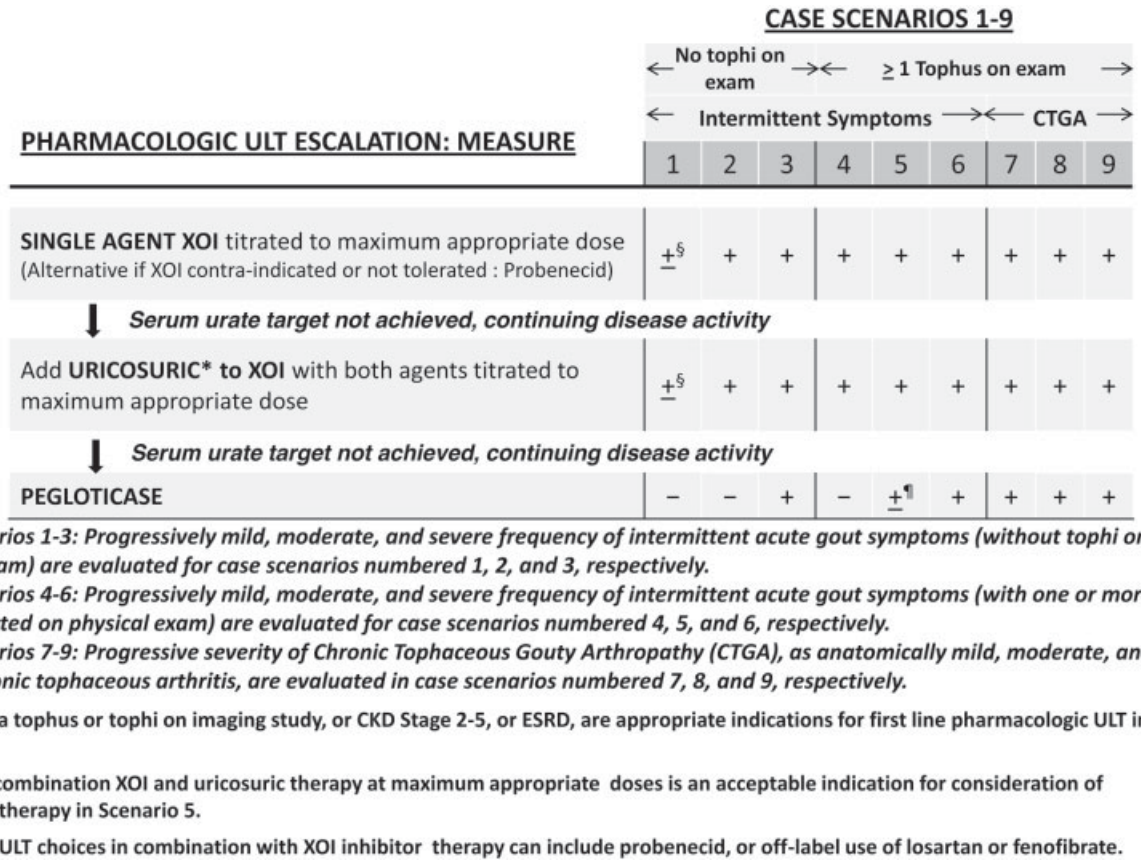
CASE SCENARIOS 1-9
No tophi on exam
≥ 1 Tophus on exam
Intermittent Symptoms
CTGA
PHARMACOLOGIC ULT ESCALATION: MEASURE
1 2 3 4 5 6 7 8 9
SINGLE AGENT XOI titrated to maximum appropriate dose
(Alternative if XOI contra-indicated or not tolerated : Probenecid)
± § + + + + + + + +
Serum urate target not achieved, continuing disease activity
Add URICOSURIC* to XOI with both agents titrated to maximum appropriate dose
± § + + + + + + + +
Serum urate target not achieved, continuing disease activity
PEGLOTICASE
– – + – ± ¶ + + + +
Case Scenarios 1-3: Progressively mild, moderate, and severe frequency of intermittent acute gout symptoms (without tophi on physical exam) are evaluated for case scenarios numbered 1, 2, and 3, respectively.
Case Scenarios 4-6: Progressively mild, moderate, and severe frequency of intermittent acute gout symptoms (with one or more tophi detected on physical exam) are evaluated for case scenarios numbered 4, 5, and 6, respectively.
Case Scenarios 7-9: Progressive severity of Chronic Tophaceous Gouty Arthropathy (CTGA), as anatomically mild, moderate, and severe chronic tophaceous arthritis, are evaluated in case scenarios numbered 7, 8, and 9, respectively.
§ Finding of a tophus or tophi on imaging study, or CKD Stage 2-5, or ESRD, are appropriate indications for first line pharmacologic ULT in Scenario 1.
¶ Failure of combination XOI and uricosuric therapy at maximum appropriate doses is an acceptable indication for consideration of Pegloticase therapy in Scenario 5.
*Uricosuric ULT choices in combination with XOI inhibitor therapy can include probenecid, or off-label use of losartan or fenofibrate.

Figure 5. Case scenario–specific escalation of pharmacologic urate-lowering therapy (ULT) in gout, including approach to refractory disease. The figure, which accompanies Table 4, shows task force panel (TFP) recommendations for patients with continuing gout disease activity and focuses on escalating pharmacologic ULT measures, particularly for refractory disease. Each of the fundamental case scenarios is considered. Case scenario numbering of 1–9 refers to those gout clinical scenarios specifically detailed in Figures 1A and B above. The chronic tophaceous gouty arthropathy (CTGA) case scenarios numbered 7–9 are additionally shown in photographs in Figure 2. These recommendations specifically assume that for each case scenario: 1) the serum urate target needed to achieve improved gout signs and symptoms has not yet been achieved, 2) appropriate nonpharmacologic ULT measures have been applied, and 3) appropriate treatment and antiinflammatory prophylaxis are employed for attacks of acute gouty arthritis. Evidence grades for individual TFP votes to recommend that are shown here are summarized in the text. In the figure, the decision-making symbol + indicates therapeutic appropriateness, with − indicative of either a therapeutically inappropriate measure or one with uncertain risk:benefit ratio. The decision-making symbol ± indicates that the TFP recommended this therapeutic measure as appropriate only in specific conditions in a clinical scenario, marked by the symbol § or ¶ that refers to particular circumstances described below the figure. CKD = chronic kidney disease; ESRD = end-stage renal disease; XOI = xanthine oxidase inhibitor.

Table 4. Summary of recommendations for case scenarios of refractory disease in gout (Figure 5), including combination oral ULT and use of pegloticase*

Attempt upward dose titration of 1 XOI to respective maximum appropriate dose (evidence A)
Febuxostat can be substituted for allopurinol or vice versa in the event of drug intolerance and adverse events, and such a substitution should be considered after initial failure of upward dose titration of 1 XOI (evidence C)†
Effective therapeutic options include addition of a uricosuric agent (e.g., probenecid, fenofibrate, or losartan) to an XOI drug (evidence B) or vice versa (evidence C)
Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, conventional and appropriately dosed ULT (evidence A)‡
Pegloticase therapy is not recommended as first-line ULT agent for any case scenarios
LACK OF CONSENSUS: appropriate duration of pegloticase therapy relative to intended and achieved decrease in symptoms and signs of gout, including decrease in tophus size

* ULT = urate-lowering therapy; XOI = xanthine oxidase inhibitor.
† Important drug label information includes that febuxostat and allopurinol should not be used in combination with each other.
‡ Important drug label information includes that pharmacologic oral ULT agents should be discontinued during the course of pegloticase therapy to avoid masking the loss of a pegloticase serum urate–lowering effect associated with an increased risk of pegloticase infusion reactions.

The TFP also weighed the rapidly emerging area of pharmacogenetics to screen for AHS (53,57,58), and recommended that, prior to initiation of allopurinol, HLA–B*5801 testing should be considered in select patient subpopulations at an elevated risk for AHS (evidence A). Those with HLA–B*5801 and of Korean descent with stage 3 or worse CKD (HLA–B*5801 allele frequency ~12%), or of Han Chinese or Thai extraction irrespective of renal function (HLA–B*5801 allele frequency ~6–8%), have been highlighted in the literature as prime examples of subjects at high risk for AHS, marked by HLA–B*5801 hazard ratios of several hundred (59–61). Such high-risk individuals were recommended to be prescribed an alternative to allopurinol if HLA–B*5801 positive (evidence A). The TFP recommended that the HLA–B*5801 screening be done by the rapid, widely available polymerase chain reaction (PCR)–based approach (evidence A) that, in only ~10% of tests, requires more cumbersome followup HLA–B*5801 sequencing for inconclusive results. Significantly, the TFP did not recommend universal HLA–B*5801 allopurinol screening. Current evidence informing this TFP decision included that whites with an HLA–B*5801 prevalence of ~2% had a substantially lower HLA–B*5801 hazard ratio and negative predictive value of the test than in the aforementioned Asian subpopulations (53,58,62).

Recommendations specific to primary uricosuric urate-lowering monotherapy. Under conditions where uricosuric monotherapy was employed as a primary ULT modality (Table 3), probenecid was recommended by the TFP as the first choice among uricosuric drugs currently available in the US (evidence B). The TFP recommended that a history of urolithiasis contraindicates first-line use of a potent uricosuric agent for ULT (evidence C), given that probenecid (and benzbromarone, which is unavailable in the US) was associated with an ~9–11% risk of urolithiasis (63,64). Specific TFP recommendations for risk management in uricosuric ULT also included initial measurement and monitoring of urine uric acid, and that an elevated urine uric acid level indicative of uric acid overproduction contraindicates uricosuric ULT. There was no TFP consensus on assay of undissociated urine uric acid, or use of Simkin's Index and similar calculation on spot urine, in risk management in uricosuric therapy (63). The TFP did recommend that when initiating uricosuric ULT, patients should also be instructed to increase fluid intake and consider urine alkalinization (e.g., with potassium citrate; evidence C for all) (63), but no quantitative parameters were voted on for these measures, in view of lack of evidence.

Recommendations on pharmacologic ULT decision making in gout, including case scenarios with mild, moderate, or severe disease activity or CTGA. The TFP voted on clinical decision making in each of the 9 case scenarios when the serum urate target had not yet been met and under circumstances where gout remained symptomatic (i.e., where there were 1 or more continuing clinical signs and symptoms of gout, such as recent acute gout attacks, tophi, and chronic gouty arthritis) (Figure 5 and Table 4). In doing so, the TFP, in limited voting scenarios, first considered the potential role of imaging in the evaluation of disease burden and clinical decision making on ULT gout. The TFP recommended the utility of high-resolution ultrasound, CT, or dual-energy CT (evidence B) to detect tophi, and the utility of plain radiographic findings consistent with tophi (such as characteristic bone erosion; evidence C). The TFP also voted that the ultrasound "double contour sign" was consistent with nontophaceous urate crystal deposition on the surface of articular cartilage (evidence B). However, the TFP did not recommend use of the double contour sign as a sufficient indicator for initiating or increasing the intensity of ULT, given that the sign was detected in joints of ~25% subjects with asymptomatic hyperuricemia in a recent study (65). Conversely, in a recent study, the double contour sign was not universally detectable (i.e., absent in ~33% of subjects in an ultrasound survey of multiple joints in each subject) in patients with early gout not receiving ULT (66).

For all 9 case scenarios when the serum urate target has not been met, the TFP recommended upward dose titration of 1 XOI (allopurinol or febuxostat) to the respective maximum appropriate dose for the individual patient (evidence A) (Figure 5 and Table 4). The maximum FDA-approved dose of allopurinol is 800 mg daily, and for febuxostat is 80 mg daily. Given the request for an international frame of the gout guidelines by the ACR, the TFP recommended increasing febuxostat up to 120 mg daily, a dose approved in many countries outside the US, in the specific scenario of active disease refractory to appropriately dosed oral ULT (evidence A). The TFP further recommended, and broadly so in the 9 case scenarios, that if upward titration of the initial XOI agent was not tolerated or did not achieve the serum urate target, substitution of another XOI was an appropriate first-line option (evidence C).

Notably, the TFP recommended probenecid and other agents with clinically significant uricosuric effects, such as fenofibrate and losartan, as therapeutically useful in a comprehensive ULT program in refractory disease (evidence B). Specifically, the TFP recommended a combination oral ULT approach (i.e., 1 XOI agent [allopurinol or febuxostat] and 1 uricosuric agent [probenecid, fenofibrate, or losartan being the currently available agents in the US]) as an option when the serum urate target has not been met across the 9 case scenarios (evidence B) (67–69) (Figure 5 and Table 4).

Last, the TFP recommended pegloticase as appropriate only in the case scenarios with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULT options (evidence A) (Figure 5 and Table 4). In 2 large placebo-controlled randomized clinical trials, pegloticase 8 mg every 2 weeks was effective in reducing the serum uric acid level to <6 mg/dl in 42% of patients versus 0% in the placebo group at 6 months (27). In addition, 45% of patients receiving pegloticase 8 mg every 2 weeks had complete resolution of 1 or more tophi versus 8% in the placebo group, with significant improvement in chronic arthropathy and health-related quality of life. Importantly, the TFP did not recommend pegloticase as a first-line ULT for any case scenarios. The TFP also did not

achieve consensus on the appropriate duration of pegloticase therapy once decreased symptoms and signs of gout, including decrease in size (or resolution) of tophi on clinical examination, had been achieved.

Discussion

We present the first ACR evidence- and consensus-based pharmacologic and nonpharmacologic management recommendations for gout, the product of a formal group consensus process. The thorough systematic review of the literature essential to this project was timely. Comparable gout guidelines independently (i.e., not developed with pharmaceutical company support) assembled at the level of national and multinational rheumatology societies in the last decade by EULAR and the BSR did not comprehensively evaluate newer evidence and therapies, including febuxostat and pegloticase (21,24). The ACR-sponsored work presented here in part 1 of the guidelines focused on systematic disease management and urate-lowering measures in all gout patients and in refractory disease, including CTGA. The work first addressed core aspects of patient education, which includes discussion with the patient of the role of uric acid excess in gout and as key long-term treatment target, and impacts heavily on ULT treatment adherence and ultimate efficacy (34). Based on the existing evidence in patients with gout, the TFP was able to generate a set of diet and lifestyle recommendations for gout, but the recommendations are dominated or superseded, for good reason, by diet and lifestyle recommendations for life-threatening comorbidities common in gout patients, such as atherosclerosis, diabetes mellitus, and hypertension. There was only limited advice on specific serving sizes and quantities, as was the case for prior gout recommendations of this nature (21). Clearly, more research is needed in diet and lifestyle modifications for gout, especially for direct intervention studies (34).

The TFP also recommended that all gout patients have a thorough clinical evaluation of disease activity and burden, and appropriate attention to possible etiologies of hyperuricemia in each patient, with potential modification of secondary causes of hyperuricemia such as comorbidities and specific medications that elevate serum urate. However, the TFP did not vote on specific indications for employing imaging studies to assess disease burden or treatment responses in gout. This issue should be updated in the next few years, as more studies appear on the use of high-resolution ultrasound and dual-energy CT that may inform disease classification and prognosis in gout, and as more outcomes data emerge on ULT-induced alterations in imaging findings of gout (70).

Specific TFP recommendations on indications for pharmacologic ULT initiation were accompanied by novel TFP recommendations that either allopurinol or febuxostat is appropriate as the first line of pharmacologic ULT, although the issue of allopurinol nontitration in comparison to clinical trial designs for these agents was recognized. Probenecid was recommended as an alternative first-line therapy if at least 1 XOI drug was contraindicated or not tolerated, but probenecid monotherapy was not recommended as a first-line approach in those with a creatinine clearance less than 50 ml/minute. In discussion, TFP reservations on probenecid included lack of data on long-term safety and efficacy in stage 3 CKD (given that creatinine clearance <50 ml/minute was an exclusion criterion in some studies [48,69]). Reservations also included multiple drug interactions, the ~9% risk of urolithiasis, and the complexity of risk management in dose escalation of probenecid ULT as a monotherapy. There was an unexpected lack of TFP consensus on ideal approaches to monitor uric acid excretion to lessen the risk of urolithiasis risk management during probenecid ULT as monotherapy.

Treating to a serum urate target was evaluated in detail. The TFP consolidated previous EULAR and BSR recommendations (21,24), here recommending that serum urate should be lowered in patients with gout to achieve, at a minimum, a serum urate level <6 mg/dl. In those with greater disease severity and urate burden, such as those with tophi detected on physical examination and with CTGA, the TFP recommended that the serum urate level may need to be lowered below 5 mg/dl to achieve better disease control.

Dosing, efficacy, and safety of allopurinol were addressed at length, since allopurinol is the most commonly prescribed ULT worldwide. First, TFP recommendations reinforced both the previous EULAR guidelines (21) and FDA guidance for risk management to initiate allopurinol at no more than 100 mg daily, and to start allopurinol at 50 mg daily in patients with stage 4 or worse CKD. Second, the TFP recommended steady upward titration of allopurinol soon after initiation, accompanied by adequate patient education and monitoring for drug toxicity. Recent clinical trial evidence that allopurinol doses of 300 mg or less daily fail to achieve target serum urate in the majority of gout patients informed the TFP recommendation that, with appropriate risk management, allopurinol can be advanced above 300 mg daily to achieve the serum urate target, including in patients with CKD. The TFP, for all degrees of renal impairment, did not recommend the AHS risk management strategy of Hande et al (56), in which a non–evidence-based algorithm for allopurinol maintenance dosing had been calibrated to renal impairment. However, the authors, without a specific TFP vote, are concerned about the lack of long-term safety data for allopurinol dosing above 300 mg daily, particularly with significant renal impairment, which is associated with increased allopurinol toxicity (50,71).

The TFP also made the novel recommendation that rapid PCR-based HLA–B*5801 screening should be considered as a risk management component in subpopulations where both the HLA–B*5801 allele frequency is elevated and the HLA–B*5801–positive subjects have a very high hazard ratio ("high risk") for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 [or worse] CKD and all those of Han Chinese and Thai descent). It is anticipated that additional high-risk subpopulations for AHS will be identified in future studies.

The TFP recommended uricosuric therapy as a valuable component of comprehensive urate-lowering strategies. Specific novel TFP recommendations on appropriateness of use of combination XOI and uricosuric ULT as a second-line approach in refractory disease across the case scenarios studied here reinforce BSR recommendations on such

a combination therapy (24). Significantly, for combination with an XOI drug, the TFP recommended not simply probenecid, but also as alternatives, other medications with less marked uricosuric effects (fenofibrate and losartan). However, the authors recognize that the published data are limited. The authors believe that ongoing and further studies will help understand how to optimize combinations of uricosuric agents with XOI therapy to decrease the risk of uricosuric-induced urolithiasis, while increasing the velocity of size reduction of body urate stores and tophi (67).

Based on results of placebo-controlled trials in study populations with particularly severe gout, the TFP recommended pegloticase as a third-line agent in distinct case scenarios of refractory disease with failure of appropriately dosed oral ULT, including in CTGA. Clinical trials directly comparing pegloticase to appropriate maximally dosed first- and second-line oral medication regimens of the agents recommended here would be of interest in severe gout, including CTGA.

Limitations of the ACR gout guidelines include the quality and quantity of evidence evaluated. For part 1 of the gout guidelines, the majority of evidence reviewed, upon which recommendations were based, was level C, with less than 20% level A evidence. For ULT clinical trials, study designs comparing allopurinol to febuxostat, where both agents are titrated to attempt to achieve the serum urate target, would be more informative than past trials (26,72,73). Another issue was variability in end points and outcome measures (e.g., gout attack frequency, serum urate, tophus size reduction, and health-related quality of life) in the clinical trials reviewed. Moreover, there are likely differences in "real-world" patients compared to those in most large industry-sponsored clinical trials. Clearly, further studies are needed in both the ULT and CTGA domains of gout.

The RAND/UCLA methodology utilized for this project did not allow us to address the important clinical practice and societal implications of treatment costs, which clearly impact patient and provider preferences for gout management options recommended by the TFP as effective. For example, the authors recognize the potential cost issues of the ULT recommendations presented, since, for example, febuxostat is substantially more expensive than allopurinol or probenecid. We note that a recent single technology appraisal with cost analysis done by an independent evidence review group of the National Institute for Health and Clinical Excellence concluded that febuxostat should be recommended for ULT in gout only in patients with contraindications or intolerance to allopurinol (25). Conversely, PCR-based HLA–B*5801 pharmacogenetics screening for allopurinol is a one-time test and relatively inexpensive, but raises new questions about the added costs to gout management, particularly for populations where the risk of AHS is low (53,57,58). Last, third-line ULT with pegloticase is an expensive biologic therapy approach for gout, and additional biologic agents for gout therapy are currently being developed and investigated. Cost-effectiveness trials and analyses are particularly timely for emerging therapies in gout.

The ACR guidelines for ULT in gout presented herein, and for treatment and antiinflammatory prophylaxis of gouty arthritis presented in a separate article (part 2 of the guidelines) (17), will require updating as new evidence emerges for appropriate evaluation and management of gout advances and new medications achieve regulatory agency approval. Increased comparative studies of gout-specific health-related quality of life impairment and disease activity outcomes for ULT agents and regimens evaluated here will be of particular interest, given cost, long-term safety, and other considerations such as cardiovascular disease outcomes. It is hoped that publication of these guidelines, along with effective patient education in gout treatments and the objectives and safety issues of management, will improve patient adherence, quality of care, and outcomes in management of gout.

Addendum. Therapies that were approved after the original literature review, or diet and lifestyle measures studied after the original literature review, are not included in these recommendations.

ACKNOWLEDGMENTS

We thank Ms Amy Miller and Ms Regina Parker of the ACR for administrative support and guidance. Drs. Jennifer Grossman (UCLA), Michael Weinblatt (Brigham and Women's Hospital, Harvard Medical School), Ken Saag (University of Alabama, Birmingham), and Ted Ganiats (University of California, San Diego) provided valuable guidance on the objectives and process. Rikke Ogawa (UCLA) provided greatly appreciated service as a medical research librarian.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Terkeltaub had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Arthritis Care & Research
Vol. 64, No. 10, October 2012, pp 1447–1461
DOI 10.1002/acr.21773
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SPECIAL ARTICLE

2012 American College of Rheumatology Guidelines for Management of Gout. Part 2: Therapy and Antiinflammatory Prophylaxis of Acute Gouty Arthritis

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Introduction

In response to a request for proposal from the American College of Rheumatology (ACR), our group was charged with developing nonpharmacologic and pharmacologic guidelines for treatments in gout that are safe and effective, i.e., with an acceptable risk/benefit ratio. These guidelines for the management and antiinflammatory prophylaxis of acute attacks of gouty arthritis complement our article on

Supported by a research grant from the American College of Rheumatology and by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant K24-AR-063120).

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Significance & Innovations

- An acute gouty arthritis attack should be treated with pharmacologic therapy, initiated within 24 hours of onset.
- Established pharmacologic urate-lowering therapy should be continued, without interruption, during an acute attack of gout.
- Nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, or oral colchicine are appropriate first-line options for treatment of acute gout, and certain combinations can be employed for severe or refractory attacks.
- Pharmacologic antiinflammatory prophylaxis is recommended for all gout patients when pharmacologic urate lowering is initiated, and should be continued if there is any clinical evidence of continuing gout disease activity and/or the serum urate target has not yet been achieved.
- Oral colchicine is an appropriate first-line gout attack prophylaxis therapy, including with appropriate dose adjustment in chronic kidney disease and for drug interactions, unless there is a lack of tolerance or medical contraindication.
- Low-dose NSAID therapy is an appropriate choice for first-line gout attack prophylaxis, unless there is a lack of tolerance or medical contraindication.

guidelines to treat hyperuricemia in patients with evidence of gout (or gouty arthritis) (1).

Gout is the most common cause of inflammatory arthritis in adults in the US. Clinical manifestations in joints and bursa are superimposed on local tissue deposition of monosodium urate crystals. Acute gout characteristically presents as a self-limited attack of synovitis (also called "gout flare"). Acute gout attacks account for a major component of the reported decreased health-related quality of life in patients with gout (2,3). Acute gout attacks can be debilitating and are associated with decreased work productivity (4,5).

Urate-lowering therapy (ULT) is a cornerstone in the management of gout (1) and, when effective in lowering serum urate, is associated with a decreased risk of acute gouty attacks (6). However, during the initial phase of ULT, there is an early increase in acute gout attacks, which has been hypothesized due to remodeling of articular urate crystal deposits as a result of rapid and substantial lowering of ambient urate concentrations (7). Acute gout attacks attributable to the initiation of ULT may contribute to nonadherence in long-term gout treatment, as reported in recent studies (8).

In order to systematically evaluate management of acute gouty arthritis, we generated multifaceted case scenarios to elucidate decision making based primarily on clinical and laboratory test–based data that can be obtained from a gout patient by both nonspecialist and specialist health care providers in an office practice setting. This effort was not intended to create a novel classification system of gout or new gout diagnostic criteria, since such endeavors are beyond the scope of this work.

Prior gout recommendations and guidelines, at the independent (i.e., non–pharmaceutical industry sponsored) national or multinational rheumatology society level, have

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Submitted for publication January 9, 2012; accepted in revised form June 15, 2012.

been published by the European League Against Rheumatism (EULAR) (9,10), the Dutch College of General Practitioners (11), and the British Society for Rheumatology (BSR) (12). The ACR requested new guidelines in view of the increasing prevalence of gout (13), the clinical complexity of management of gouty arthritis imposed by comorbidities common in patients with gout (14), and increasing numbers of treatment options via clinical development of agents (15–17). The ACR charged us to develop these guidelines to be useful for both rheumatologists and other health care providers on an international level. As such, this process and resultant recommendations involved a diverse and international panel of experts.

In this article, we concentrate on 2 of the 4 gout domains (1) that the ACR requested for evaluation of pharmacologic and nonpharmacologic management approaches: analgesic and antiinflammatory management of acute attacks of gouty arthritis and pharmacologic antiinflammatory prophylaxis of acute attacks of gouty arthritis. Part 1 of the guidelines focused on systematic nonpharmacologic measures (patient education, diet and lifestyle choices, identification and management of comorbidities) that impact hyperuricemia, and made recommendations on pharmacologic ULT in a range of case scenarios of patients with disease activity manifested by acute and chronic forms of gouty arthritis, including chronic tophaceous gouty arthropathy (1). Each individual and specific statement is designated as a "recommendation," in order to reflect the nonprescriptive nature of decision making for the hypothetical clinical scenarios.

So that the voting panel could focus on gout treatment decisions, a number of key assumptions were made, as described in part 1 of the guidelines (1). Importantly, each proposed recommendation assumed that correct diagnoses of gout and acute gouty arthritis attacks had been made for the voting scenario in question. For treatment purposes, it was also assumed that treating clinicians were competent, and considered underlying medical comorbidities (including diabetes mellitus, gastrointestinal disease, hypertension, and hepatic, cardiac, and renal disease) and potential drug toxicities and drug–drug interactions when making both treatment choices and dosing decisions on chosen pharmacologic interventions. The RAND/University of California at Los Angeles (UCLA) methodology used here emphasizes the level of evidence, safety, and quality of therapy, and excludes analyses of societal cost of health care. As such, the ACR gout guidelines are designed to reflect best practice, supported either by level of evidence or consensus-based decision making. These guidelines cannot substitute for individualized direct assessment of the patient, coupled with clinical decision making by a competent health care practitioner. The motivation, financial circumstances, and preferences of the gout patient also need to be considered in clinical practice, and it is incumbent on the treating clinician to weigh the issues not addressed by this methodology, such as treatment costs, when making management decisions. Last, the guidelines for gout management presented herein were not designed to determine eligibility for health care cost coverage by third party payors.

Materials and methods

Utilizing the RAND/UCLA methodology (18), we conducted a systematic review, generated case scenarios, developed recommendations, and graded the evidence.

Design: RAND/UCLA Appropriateness Method overview. The RAND/UCLA method of group consensus was developed in the 1980s, incorporates both Delphi and nominal group methods (18), and has been successfully used to develop other guidelines commissioned by the ACR. The purpose of this methodology is to reach a consensus among experts, with an understanding that published literature may not be adequate to provide sufficient evidence for day-to-day clinical decision making. The RAND/UCLA method requires 2 groups of experts: a core expert panel (CEP) that provides input into case scenario development, and a task force panel (TFP) that votes on the case scenarios (1). A systematic review of pertinent literature was performed concurrently, and a scientific evidence report was generated. This evidence report was then given to the TFP, in conjunction with a variety of clinical scenarios and clinical decision-making questions of interest for each scenario.

The diverse TFP, totaling 11 people, consisted of rheumatologists in a community private practice (CK), a health maintenance organization practice (GL), and a Veterans Affairs practice (GK); a rheumatology physician–scientist inflammation researcher (BR); a rheumatologist with expertise in clinical pharmacology (DEF); a rheumatologist gout expert that is an Internal Medicine Residency Director (NLE); a rheumatologist gout expert that is a Chair of Internal Medicine (BM); 2 primary care internal medicine physicians (DJ, SAY); a nephrologist (VN); and a patient representative (SK) (1). There were 2 rounds of ratings, the first anonymous, with the members of the TFP instructed to rank each potential element of the guidelines on a risk/benefit Likert scale ranging from 1–9, followed by a face-to-face group discussion with revoting. A vote of 1–3 on the Likert scale was scored as *inappropriate*, where risks clearly outweigh the benefits; a vote of 4–6 was scored as *uncertain* ("lack of consensus"), where the risk/benefit ratio is uncertain; and a vote of 7–9 was scored as *appropriate*, where benefits clearly outweigh the risks. Case scenarios were translated into recommendations, where the median voting scores were 7–9 on the Likert scale ("appropriate"), and if there was no significant disagreement, defined as no more than one-third of the TFP voting below the Likert scale level of 7 in the question. The final rating was done anonymously in a 2-day face-to-face meeting led by an experienced internal medicine physician moderator (NW).

Systematic review. PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to find all articles on gout with the help of an experienced librarian. PubMed is a database of medical literature from the 1950s to the present. CENTRAL includes references from PubMed, Embase, and the Cochrane Review Groups' specialized registers of controlled trials and hand search results. We used search terminology (hedge) based on the Cochrane Highly Sensitive Search Strategy for identifying

randomized trials. The hedge was expanded to include articles discussing research design, cohort, case–control, and cross-sectional studies. Limits added to the hedge include English language and the exclusion of "animal only" studies. The searches for all 4 domains were conducted simultaneously and therefore included terms for hyperuricemia and other gout-related issues. Conducted on September 25, 2010, the search retrieved 5,830 articles from PubMed and CENTRAL. The review was divided into 3 stages: titles, abstracts from manuscripts, and entire manuscripts. At each stage, each title, abstract, or manuscript was included or excluded using prespecified rules, as described (1). Of the 5,830 titles, 192 duplicate titles and 82 non-English titles were excluded, with an additional 3,729 titles excluded based on exclusion criteria, leaving 1,827 titles, of which another 1,699 were excluded in the abstract phase. A total of 128 manuscripts remained that were further categorized into pharmacologic and nonpharmacologic studies (1). Subsequently, we updated our systematic review by repeating the search with the same criteria to include any articles that were published between September 25, 2010 and March 31, 2011, and we hand searched recent meeting abstracts from the ACR and EULAR for any randomized controlled trials that were yet to be published. The supplemental search resulted in 4 additional manuscripts and 5 meeting abstracts on pharmacologic agents, some of which were subsequently published and then reevaluated for evidence grade. Finally, there were 41 manuscripts on nonpharmacologic modalities (such as diet, alcohol, exercise, etc.) that included both retrospective and prospective studies, but all were excluded, since none were randomized controlled studies on interventions in gout patients. There were 87 manuscripts on pharmacologic agents for the treatment of patients with gout. Of these, 47 were randomized controlled trials and included in the evidence report, whereas the remaining 40 uncontrolled trials were excluded. A total of 21 manuscripts on ULT were separately addressed (1).

For this article (part 2 of the guidelines), a total of 30 manuscripts and 5 meeting abstracts were assessed, with 26 manuscripts and 2 meeting abstracts on acute gout and 4 manuscripts and 3 meeting abstracts on prophylaxis included in the evidence report and evaluated by the TFP.

Case scenarios. Through an interactive, iterative process, the CEP developed unique case scenarios of acute gouty attacks with varied treatment options, and the type of attack by severity, duration, and extent of the attack. The objective was to represent a broad spectrum of attacks that a clinician might see in a busy practice. For the case scenarios, the severity of acute gout differed based on self-reported worst pain on a 0–10 visual analog scale (VAS) (19,20). Pain ≤4 was considered mild, 5–6 was considered moderate, and ≥7 was considered severe (19,20). Case scenarios also varied by duration of the acute gout attack; we divided this into early (<12 hours), well established (12–36 hours), and late (>36 hours). Case scenarios also varied in the number of active joints involved: 1 or a few small joints, 1 or 2 large joints (ankle, knee, wrist, elbow, hip, or shoulder), and polyarticular involvement (defined as either acute arthritis involving 3 separate large joints, or acute arthritis of 4 or more joints, with arthritis involving more than 1 "region" of joints). Joint regions were defined as: forefoot (metatarsal joints and toes), midfoot (tarsal joints), ankle/hindfoot, knee, hip, fingers, wrist, elbow, shoulder, or other (Figure 1). The management strategies presented were developed for case scenarios involving gouty arthritis, but the intent was that acute bursal inflammation due to gout (e.g., in the prepatellar or olecranon bursa) and small joint involvement would have comparable recommendations for overall management strategies.

Developing recommendations from votes by the TFP and grading the evidence. A priori recommendations were derived from only positive results (median Likert score ≥7). In the text below, all recommendations derived from TFP votes are denoted by an accompanying evidence grade. In addition to TFP vote results, the panel provided some statements based on discussion (not votes). Such statements are specifically described as discussion items (rather than TFP-voted recommendations) in the Results. We also comment on specific circumstances where the TFP did not vote a particularly important clinical decision-making item as appropriate (i.e., the median Likert score was ≤6 or there was a wide dispersion of votes despite a median score of ≥7). Samples of voting scenarios and results are shown in Supplemental Figure 1 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

The level of evidence supporting each recommendation was ranked based on previous methods used by the American College of Cardiology (21) and applied to other recent ACR recommendations (22,23): level A grading was assigned to recommendations supported by more than 1 randomized clinical trial, or 1 or more meta-analyses; level B grading was assigned to the recommendations derived from a single randomized trial, or nonrandomized studies; and level C grading was assigned to consensus opinion of experts, case studies, or standard of care.

Managing perceived potential conflict of interest (COI). Potential COI was managed in a prospective and structured manner (1). All of the participants intellectually involved in the project, whether authors or not, were required to fully disclose their relationships with any of the companies with a material interest in gout, listed in Supplemental Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Disclosures were identified at the start of the project and updated every 6 months. A summary listing of all perceived potential COI is available in Supplemental Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Based on the policies of the ACR, no more than 49% of the project participants were permitted to have COI at any given time, and a majority of the TFP was required to have no perceived potential COI. It was further required that the project principal investigator (JDF) remain without per-

Severity of Acute Gouty Arthritis Attack Intensity of attack based on self-reported pain (0-10 visual analog scale)	
Mild	≤ 4
Moderate	5-6
Severe	≥ 7

Duration of the gouty arthritis attack since onset	
Early	< 12 Hours after attack onset
Well-Established	12 to 36 Hours after attack onset
Late	> 36 Hours after attack onset

Extent of acute gouty arthritis attack Based on number of active joints
One or a few small joints
1 or 2 large* joints * *defined as: ankle, knee, wrist, elbow, hip, shoulder*
Polyarticular • 4 or more joints, with arthritis involving more than 1 region§ § *Regions defined as: forefoot (metatarsophalangeal joints, toes), midfoot (tarsal joints), ankle/hindfoot, knee, hip, fingers, wrist, elbow, shoulder, other* • Acute gout attack involving 3 separate large joints is considered as a form of polyarticular gout for this scheme of management

Figure 1. Case scenarios for defining acute gouty arthritis attack features. These case scenarios were generated by the core expert panel, and therapeutic decision-making options for these scenarios were voted on by the task force panel.

ceived potential COI during the guideline development process, and for an additional 12 months afterward.

Results

General principles for treatment of the acute attack of gouty arthritis ("acute gout" management). Figure 2 summarizes the overall recommendations on treatment of an acute gouty arthritis attack. The TFP recommended that an acute gouty arthritis attack should be treated with pharmacologic therapy (evidence C), and that treatment should be preferentially initiated within 24 hours of onset of an acute gout attack (evidence C). The latter recommendation was based on consensus that early treatment leads to better patient-reported outcomes. The TFP also recommended continuing established pharmacologic ULT without interruption during an acute attack of gout (evidence C), i.e., do not stop ULT therapy during an acute attack. The TFP also recommended patient education, not simply on dietary and other triggers of acute gout attacks, but also providing the patients with instruction so that they can initiate treatment upon signs and symptoms of an acute gout attack, without the need to consult their health care practitioner for each attack (evidence B) (24). Moreover, fundamental patient education includes discussion that gout is caused by body excess of uric acid, and that only effective ULT is potentially "curative" (evidence B) (24).

Initial pharmacologic treatment of the acute attack of gouty arthritis. The TFP recommended that the choice of pharmacologic agent should be based upon severity of pain and the number of joints involved (Figure 2). For attacks of mild/moderate gout severity (≤6 of 10 on a 0–10 pain VAS) particularly those involving 1 or a few small joints or 1 or 2 large joints, the TFP recommended that initiating monotherapy was appropriate, with recommended options being oral nonsteroidal antiinflammatory drugs (NSAIDs), systemic corticosteroids, or oral colchicine (evidence A for all therapeutic categories) (25–28) (Figure 2). The TFP also voted that combination therapy was an appropriate option to consider when the acute gout attack was characterized by severe pain, particularly in an acute polyarticular gout attack or an attack involving 1–2 large joints (evidence C) (Figure 2). The TFP did not rank one therapeutic class over another. Therefore, it is at the discretion of the prescribing physicians to choose the most appropriate monotherapy based on the patient's preference, prior response to pharmacologic therapy for an acute gout attack, and associated comorbidities. Recommendations for appropriate combination therapy options are highlighted in Table 1 and discussed below. The TFP did not vote on case scenarios for specific renal or hepatic function impairment–adjusted dosing and individual contraindications or drug–drug interactions with pharmacologic therapies (29–31).

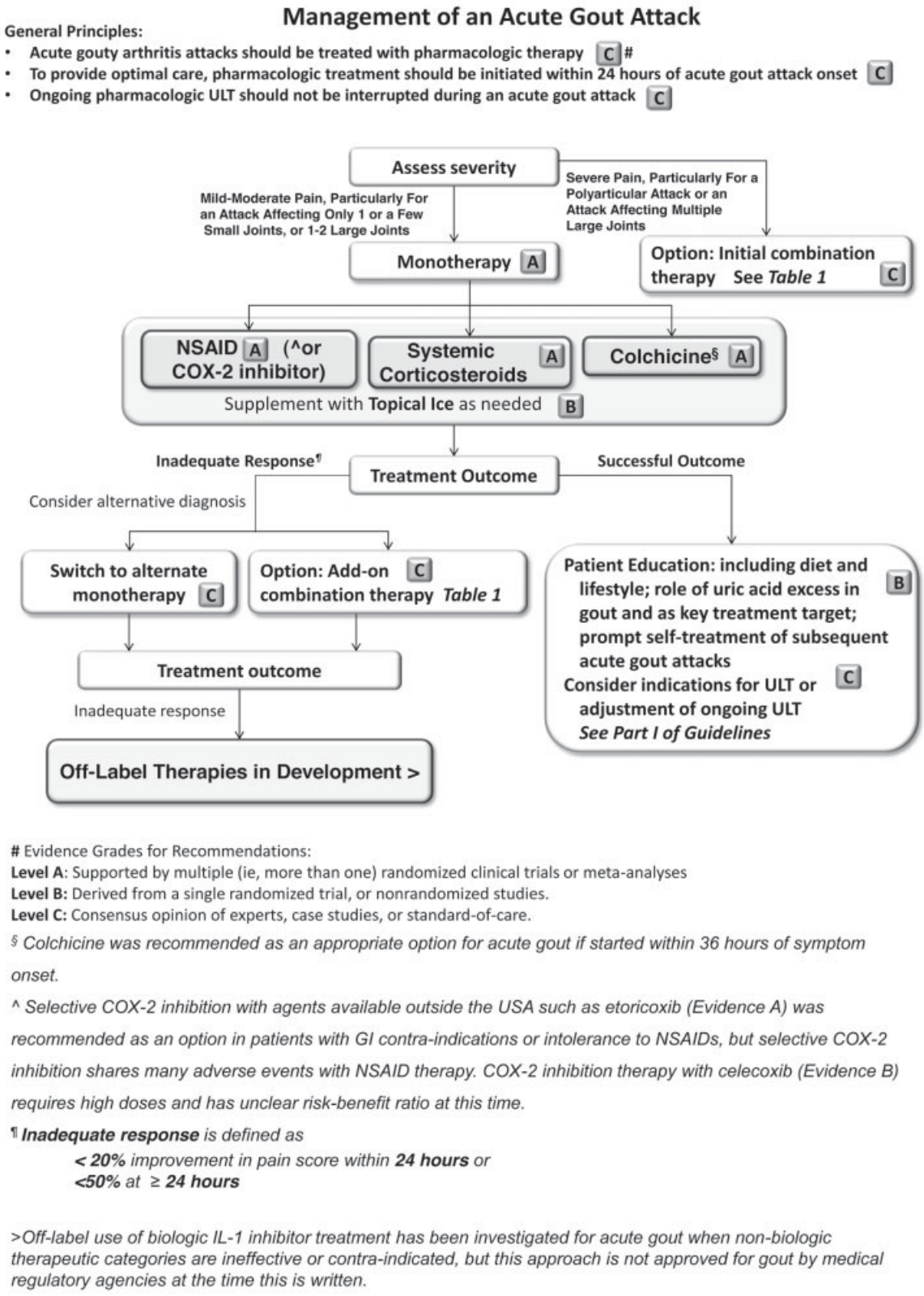

Management of an Acute Gout Attack
General Principles:
• Acute gouty arthritis attacks should be treated with pharmacologic therapy C #
• To provide optimal care, pharmacologic treatment should be initiated within 24 hours of acute gout attack onset C
• Ongoing pharmacologic ULT should not be interrupted during an acute gout attack C
Assess severity
Mild-Moderate Pain, Particularly For an Attack Affecting Only 1 or a Few Small Joints, or 1-2 Large Joints
Severe Pain, Particularly For a Polyarticular Attack or an Attack Affecting Multiple Large Joints
Monotherapy A
Option: Initial combination therapy See Table 1 C
NSAID A (^or COX-2 inhibitor)
Systemic Corticosteroids A
Colchicine§ A
Supplement with Topical Ice as needed B
Inadequate Response¶
Treatment Outcome
Successful Outcome
Consider alternative diagnosis
Switch to alternate monotherapy C
Option: Add-on C combination therapy Table 1
Patient Education: including diet and lifestyle; role of uric acid excess in gout and as key treatment target; prompt self-treatment of subsequent acute gout attacks B
Consider indications for ULT or adjustment of ongoing ULT C
See Part I of Guidelines
Treatment outcome
Inadequate response
Off-Label Therapies in Development >
Evidence Grades for Recommendations:
Level A: Supported by multiple (ie, more than one) randomized clinical trials or meta-analyses
Level B: Derived from a single randomized trial, or nonrandomized studies.
Level C: Consensus opinion of experts, case studies, or standard-of-care.
§ Colchicine was recommended as an appropriate option for acute gout if started within 36 hours of symptom onset.
^ Selective COX-2 inhibition with agents available outside the USA such as etoricoxib (Evidence A) was recommended as an option in patients with GI contra-indications or intolerance to NSAIDs, but selective COX-2 inhibition shares many adverse events with NSAID therapy. COX-2 inhibition therapy with celecoxib (Evidence B) requires high doses and has unclear risk-benefit ratio at this time.
¶ Inadequate response is defined as
< 20% improvement in pain score within 24 hours or
<50% at ≥ 24 hours
>Off-label use of biologic IL-1 inhibitor treatment has been investigated for acute gout when non-biologic therapeutic categories are ineffective or contra-indicated, but this approach is not approved for gout by medical regulatory agencies at the time this is written.

Figure 2. Overview of management of an acute gout attack. This algorithm summarizes the recommendations by the task force panel on the overall approach to management of an acute attack of gouty arthritis, with further details, as expanded in other figures and tables, referenced in the figure and discussed in the text. ULT = urate-lowering therapy; NSAID = nonsteroidal antiinflammatory drug; COX-2 = cyclooxygenase 2; GI = gastrointestinal; IL-1 = interleukin-1.

Table 1. Task force panel (TFP) recommendations for combination therapy approach to acute gouty arthritis

Initial combination therapy is an appropriate option for an acute, severe gout attack, particularly with involvement of multiple large joints or polyarticular arthritis (evidence C)
Acceptable combination therapy approaches include the initial simultaneous use of full doses (or, where appropriate, prophylaxis doses) of either: 1) colchicine and nonsteroidal antiinflammatory drugs (NSAIDs), 2) oral corticosteroids and colchicine, or 3) intra-articular steroids with all other modalities (evidence C)
For patients not responding adequately to initial pharmacologic monotherapy, adding a second appropriate agent is an acceptable option (evidence C)*
The TFP was not asked to vote on use of NSAIDs and systemic corticosteroids in combination, given core expert panel concerns about synergistic gastrointestinal tract toxicity

* Assumes that the initial diagnosis of acute gout was correct, and that the lack of adequate response of acute gout was to an appropriate first-line therapy option.

NSAIDs. For NSAIDs, the TFP recommended full dosing at either the Food and Drug Administration (FDA)– or European Medical Agency–approved antiinflammatory/analgesic doses used for the treatment of acute pain and/or treatment of acute gout (evidence A–C) (27,28,32–34) (Figure 3A). The FDA has approved naproxen (evidence A) (34,35), indomethacin (evidence A) (27,28,32,33), and sulindac (evidence B) (36) for the treatment of acute gout. However, analgesic and antiinflammatory doses of other NSAIDs may be as effective (evidence B and C). For cyclooxygenase 2 (COX-2) inhibitors, as an option in patients with gastrointestinal contraindications or intolerance to NSAIDs, published randomized controlled trials support the efficacy of etoricoxib (evidence A) and lumiracoxib (evidence B) (25,37,38), but these agents are not available in the US, and lumiracoxib has been withdrawn from use in several countries due to hepatotoxicity. A randomized controlled trial of a single comparison of celecoxib versus indomethacin (39) suggested effectiveness of a high-dose celecoxib regimen (800 mg once, followed by 400 mg on day 1, then 400 mg twice daily for a week) in acute gout. The TFP recommended this celecoxib regimen as an option for acute gout in carefully selected patients with contraindications or intolerance to NSAIDs (evidence B), keeping in mind that the risk/benefit ratio is not yet clear for celecoxib in acute gout.

The TFP did not reach a consensus to preferentially recommend any one specific NSAID as first-line treatment. The TFP did recommend continuing the initial NSAID inhibitor treatment regimen at the full dose (if appropriate) until the acute gouty attack completely resolved (evidence C). The option to taper the dose in patients with multiple comorbidities/hepatic or renal impairment was reinforced by the TFP, without specific TFP voting or more prescriptive guidance. Last, there was no TFP consensus on the use of intramuscular ketorolac or topical NSAIDs for the treatment of acute gout.

Colchicine. The TFP recommended oral colchicine as one of the appropriate primary modality options to treat acute gout, but only for gout attacks where the onset was no greater than 36 hours prior to treatment initiation (evidence C) (Figure 3B). The TFP recommended that acute gout can be treated with a loading dose of 1.2 mg of colchicine followed by 0.6 mg 1 hour later (evidence B) (10), and this regimen can then be followed by gout attack prophylaxis dosing 0.6 mg once or twice daily (unless dose adjustment is required) 12 hours later, until the gout attack resolves (evidence C) (26). For countries where 1.0 mg or 0.5 mg rather than 0.6 mg tablets of colchicine are available, the TFP recommended, as appropriate, 1.0 mg colchicine as the loading dose, followed by 0.5 mg 1 hour later, and then followed, as needed, after 12 hours, by continued colchicine (up to 0.5 mg 3 times daily) until the acute attack resolves (evidence C). In doing so, the TFP rationale was informed by pharmacokinetics of the low-dose colchicine regimen, where the exposure to the drug in plasma becomes markedly reduced ~12 hours after administration in healthy volunteers (26). The TFP also evaluated prior EULAR recommendations on a colchicine dosing regimen for acute gout (0.5 mg 3 times daily) and the BSR-recommended maximum dosage for acute gout of 2 mg colchicine per day (10,12).

The algorithm in Figure 3B outlines recommendations for colchicine based on FDA labeling and TFP deliberations and votes, including specific recommendations for patients already receiving colchicine acute gout attack prophylaxis. For more specific prescriptive guidance, practitioners should consult the FDA-approved drug labeling, including recommended dosing reduction in moderate to severe chronic kidney disease (CKD) (40,41), and colchicine dose reduction (or avoidance of colchicine use) with drug interactions with moderate to high potency inhibitors of cytochrome P450 3A4 and of P-glycoprotein; major colchicine drug interactions include those with clarithromycin, erythromycin, cyclosporine, and disulfiram (30,31). Last, the TFP did not vote on use of intravenous colchicine, since the formulation is no longer available in the US, due to misuse and associated severe toxicity.

Systemic and intraarticular corticosteroids and adrenocorticotropic hormone (ACTH). When selecting corticosteroids as the initial therapy, the TFP recommended to first consider the number of joints with active arthritis. For involvement of 1 or 2 joints, the TFP recommended the use of oral corticosteroids (evidence B); the TFP additionally recommended the option of intraarticular corticosteroids for acute gout of 1 or 2 large joints (evidence B) (42) (Figure 3C). For intraarticular corticosteroid therapy in acute gouty arthritis, it was recommended that dosing be based on the size of the involved joint(s), and that this modality could be used in combination (Table 1) with oral corticosteroids, NSAIDs, or colchicine (evidence B) (42). Specific doses for intraarticular corticosteroid therapy in specific joints were not considered during TFP voting.

Where intraarticular joint injection is impractical (e.g., polyarticular joint involvement, patient preference, or injection of the involved joint site is not in the scope of the provider's usual practice), the TFP recommended oral cor-

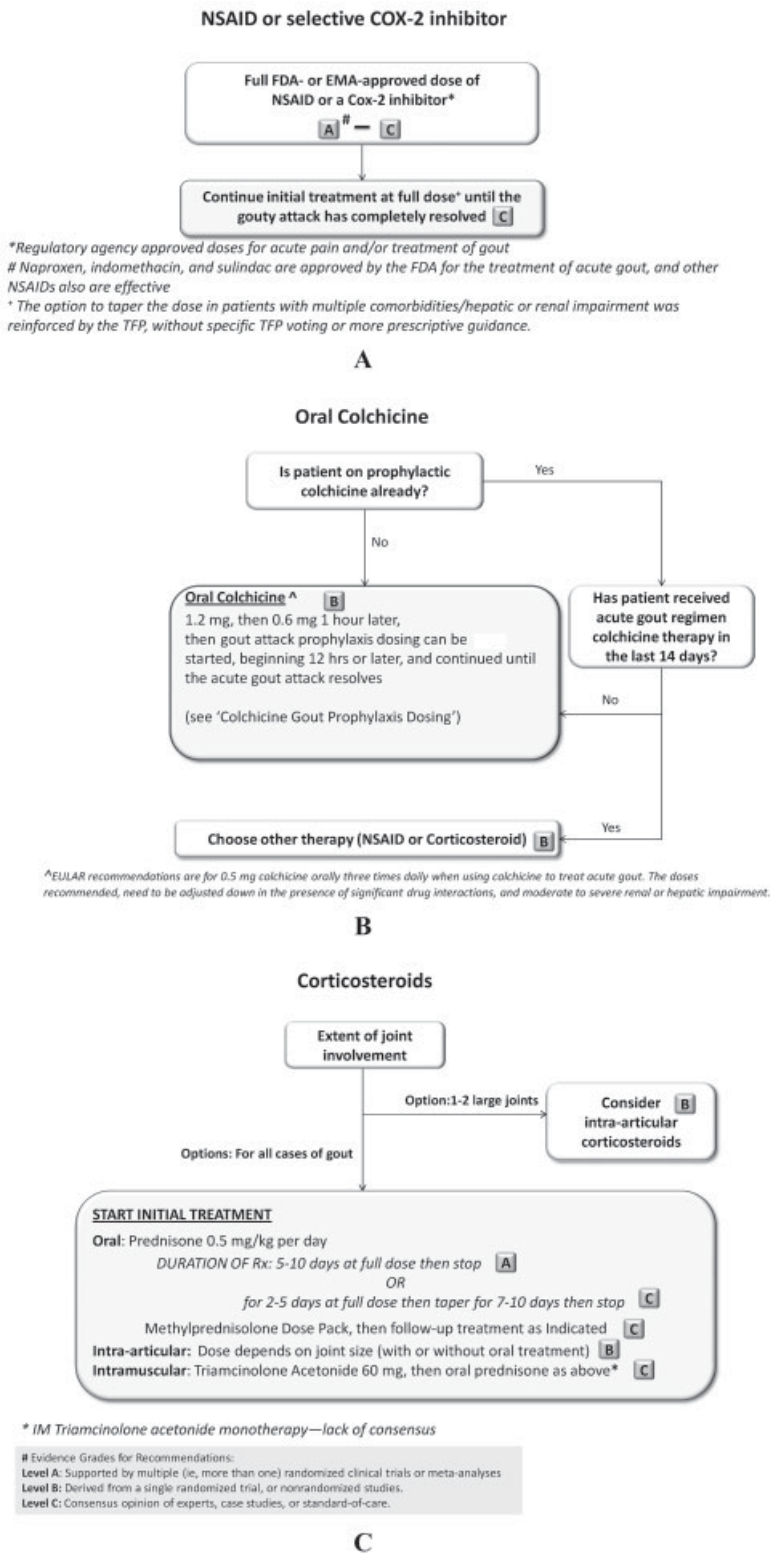
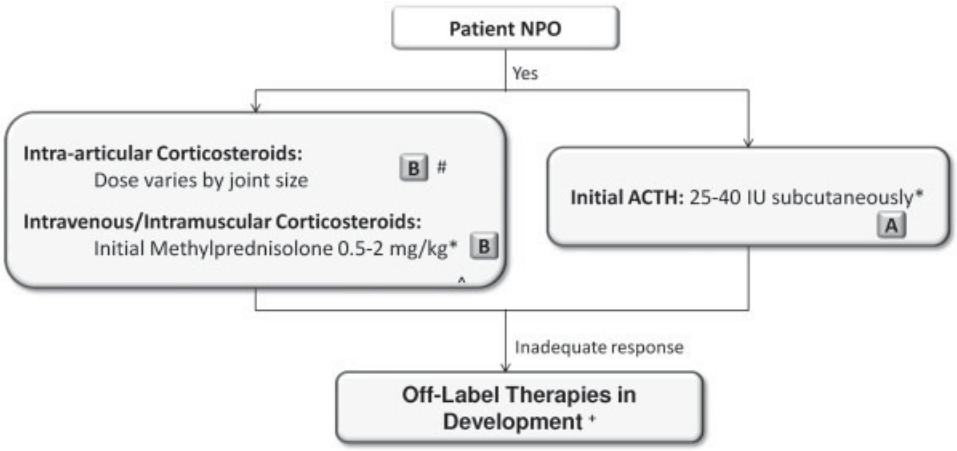

NSAID or selective COX-2 inhibitor
Full FDA- or EMA-approved dose of NSAID or a Cox-2 inhibitor*
A # – C
Continue initial treatment at full dose+ until the gouty attack has completely resolved C
*Regulatory agency approved doses for acute pain and/or treatment of gout
Naproxen, indomethacin, and sulindac are approved by the FDA for the treatment of acute gout, and other NSAIDs also are effective
+ The option to taper the dose in patients with multiple comorbidities/hepatic or renal impairment was reinforced by the TFP, without specific TFP voting or more prescriptive guidance.
A
Oral Colchicine
Is patient on prophylactic colchicine already?
Yes
No
Oral Colchicine ^ B
1.2 mg, then 0.6 mg 1 hour later, then gout attack prophylaxis dosing can be started, beginning 12 hrs or later, and continued until the acute gout attack resolves
(see 'Colchicine Gout Prophylaxis Dosing')
Has patient received acute gout regimen colchicine therapy in the last 14 days?
No
Yes
Choose other therapy (NSAID or Corticosteroid) B
^EULAR recommendations are for 0.5 mg colchicine orally three times daily when using colchicine to treat acute gout. The doses recommended, need to be adjusted down in the presence of significant drug interactions, and moderate to severe renal or hepatic impairment.
B
Corticosteroids
Extent of joint involvement
Option:1-2 large joints
Consider B intra-articular corticosteroids
Options: For all cases of gout
START INITIAL TREATMENT
Oral: Prednisone 0.5 mg/kg per day
DURATION OF Rx: 5-10 days at full dose then stop A
OR
for 2-5 days at full dose then taper for 7-10 days then stop C
Methylprednisolone Dose Pack, then follow-up treatment as Indicated C
Intra-articular: Dose depends on joint size (with or without oral treatment) B
Intramuscular: Triamcinolone Acetonide 60 mg, then oral prednisone as above* C
* IM Triamcinolone acetonide monotherapy—lack of consensus
# Evidence Grades for Recommendations:
Level A: Supported by multiple (ie, more than one) randomized clinical trials or meta-analyses
Level B: Derived from a single randomized trial, or nonrandomized studies.
Level C: Consensus opinion of experts, case studies, or standard-of-care.
C

Figure 3. Recommendations for the individual pharmacologic monotherapy options for an acute gouty arthritis attack. The figure is separated into distinct parts that schematize use of the first-line therapy options (**A,** nonsteroidal antiinflammatory drugs [NSAIDs], **B,** colchicine, and **C,** corticosteroids), and specific recommendations by the task force panel (TFP). COX-2 = cyclooxygenase 2; FDA = Food and Drug Administration; EMA = European Medical Agency; EULAR = European League Against Rheumatism; IM = intramuscular.

ticosteroids, prednisone, or prednisolone at a starting dosage of at least 0.5 mg/kg per day for 5–10 days, followed by discontinuation (evidence A) (28,43), or alternately, 2–5 days at the full dose, followed by tapering for 7–10 days, and then discontinuation (evidence C). Acknowledging current prevalence of usage, the TFP recommended, as an



** Can be repeated. Subsequent dose will be determined based on initial response.*

^Lack of consensus: IM Triamcinolone acetonide monotherapy, and IM Ketorolac NSAID therapy.

+ Off-label biologic IL-1 inhibitor treatment, such as with anakinra, has not been approved by medical regulatory agencies for gout at the time this is written, and has unclear risk-benefit ratio.

Evidence Grades for Recommendations:
Level A: Supported by multiple (ie, more than one) randomized clinical trials or meta-analyses
Level B: Derived from a single randomized trial, or nonrandomized studies.
Level C: Consensus opinion of experts, case studies, or standard-of-care.

Figure 4. Acute gouty arthritis attack management in the nothing by mouth (NPO) patient. The figure schematizes options for management of acute gout in the patient unable to take oral antiinflammatory medications, and specific recommendations by the task force panel on decision making in this setting. ACTH = adrenocorticotropic hormone; IL-1 = interleukin-1; IM = intramuscular; NSAID = nonsteroidal antiinflammatory drug.

appropriate option according to provider and patient preference, the use of an oral methylprednisolone dose pack for initial treatment of an acute attack of gout (evidence C).

The TFP also recommended, as appropriate in each case scenario, an alternative regimen of intramuscular single-dose (60 mg) triamcinolone acetonide, followed by oral prednisone or prednisolone (evidence C). However, there was no consensus by the TFP on the use of intramuscular triamcinolone acetonide as monotherapy. Last, the TFP vote also did not reach a consensus on use of ACTH (evidence A) for acute gout in patients able to take medications orally, but did consider ACTH in separate voting, as described below, for patients unable to take oral antiinflammatory medications.

Initial combination therapy for acute gout. For patients with severe acute gout attack (≥7 of 10 on a 0–10 pain VAS) and patients with an acute polyarthritis or involvement of more than 1 large joint, the TFP recommended, as an appropriate option, the initial simultaneous use of full doses (or, where appropriate, a full dose of 1 agent and prophylaxis dosing of the other) of 2 of the pharmacologic modalities recommended above. Specifically, the TFP recommended the option to use combinations of colchicine and NSAIDs, oral corticosteroids and colchicine, or intra-articular steroids with any of the other modalities (evidence C). The TFP was not asked by the CEP to vote on use of NSAIDs and systemic corticosteroids in combination, given CEP concerns about synergistic gastrointestinal tract toxicity of that drug combination.

Inadequate response of an acute gout attack to initial therapy. There is a lack of a uniform definition of an inadequate response to the initial pharmacologic therapy for an acute attack of gouty arthritis (2,26,44). Clinical trials in acute gout have defined variable primary end points for therapeutic response, such as percent improvement in pain on a Likert scale or VAS. To define inadequate response for scenarios in this section, the CEP asked the TFP to vote on various percent improvement definitions at time points such as 24, 48, or 72 hours. The TFP voted that the following criteria would define an inadequate response of acute gout to pharmacologic therapy in case scenarios: either <20% improvement in pain score within 24 hours or <50% improvement in pain score ≥24 hours after initiating pharmacologic therapy.

For the scenario of a patient with an acute attack of gouty arthritis not responding adequately to initial pharmacologic monotherapy, the TFP advised, without a specific vote, that alternative diagnoses to gout should be considered (Figure 2 and Table 1). For patients not responding to initial therapy, the TFP also recommended switching to another monotherapy recommended above (evidence C) or adding a second recommended agent (evidence C). Use of a biologic interleukin-1 (IL-1) inhibitor (anakinra 100 mg subcutaneously daily for 3 consecutive

days; evidence B) (44,45) or canakinumab 150 mg subcutaneously (46,47) as an option for severe attacks of acute gouty arthritis refractory to other agents was graded as evidence A in the systematic review. Given a lack of randomized studies for anakinra (44,45) and the unclear risk/benefit ratio and lack of FDA approval for canakinumab (46,47) at the time this was written, the authors, independent of TFP discussion, assessed the role of IL-1 inhibitor therapy in acute gout as uncertain.

Case scenarios for the nothing by mouth (NPO) patient. Acute gout attacks are common in the in-hospital setting, where patients may be NPO due to different surgical and medical conditions. In such a scenario, the TFP recommended intraarticular injection of corticosteroids for involvement of 1 or 2 joints (with the dose depending on the size of the joint; evidence B) (42) (Figure 4). The TFP also recommended, as appropriate options, intravenous or intramuscular methylprednisolone at an initial dose at 0.5–2.0 mg/kg (evidence B) (48).

The TFP also recommended, as an appropriate alternative for the NPO patient, subcutaneous synthetic ACTH at an initial dose of 25–40 IU (evidence A) (49), with repeat doses as clinically indicated (for either ACTH or intravenous steroid regimens). There was no voting by the TFP on specific followup ACTH or an intravenous steroid dosing regimen, given a lack of evidence. In the scenario of the NPO patient with acute gout, there was no consensus on the use of intramuscular ketorolac or intramuscular triamcinolone acetonide monotherapy. Biologic IL-1 inhibition therapy remains an FDA-unapproved modality for NPO patients, without specific past evaluation in this population.

Critical drug therapy adverse event considerations in acute gout. It was not possible to evaluate every permutation of gout treatment and comorbid disease, given the constraints of the project. The treating clinician will need to carefully weigh the complexities of each unique patient. TFP discussions emphasized that potential drug toxicities due to comorbidities and drug–drug interactions are considerable in treatment of acute gout (30,31). Some examples include underlying moderate and severe CKD (NSAIDs, COX-2 inhibitors, colchicine), congestive heart failure (NSAIDs, COX-2 inhibitors), peptic ulcer disease (NSAIDs, COX-2 inhibitors, corticosteroids), anticoagulation or antiplatelet aggregation therapy (NSAIDs), diabetes mellitus (corticosteroids), ongoing infection or high risk of infection (corticosteroids), and hepatic disease (NSAIDs, COX-2 inhibitors, colchicine) (30,31).

Complementary therapies for acute gout attack. The TFP recommended topical ice application to be an appropriate adjunctive measure to 1 or more pharmacologic therapies for acute gouty arthritis (evidence B) (50). The TFP voted, as inappropriate, the use of a variety of oral complementary agents for the treatment of an acute attack (cherry juice or extract, salicylate-rich willow bark extract, ginger, flaxseed, charcoal, strawberries, black currant, burdock, sour cream, olive oil, horsetail, pears, or celery root).

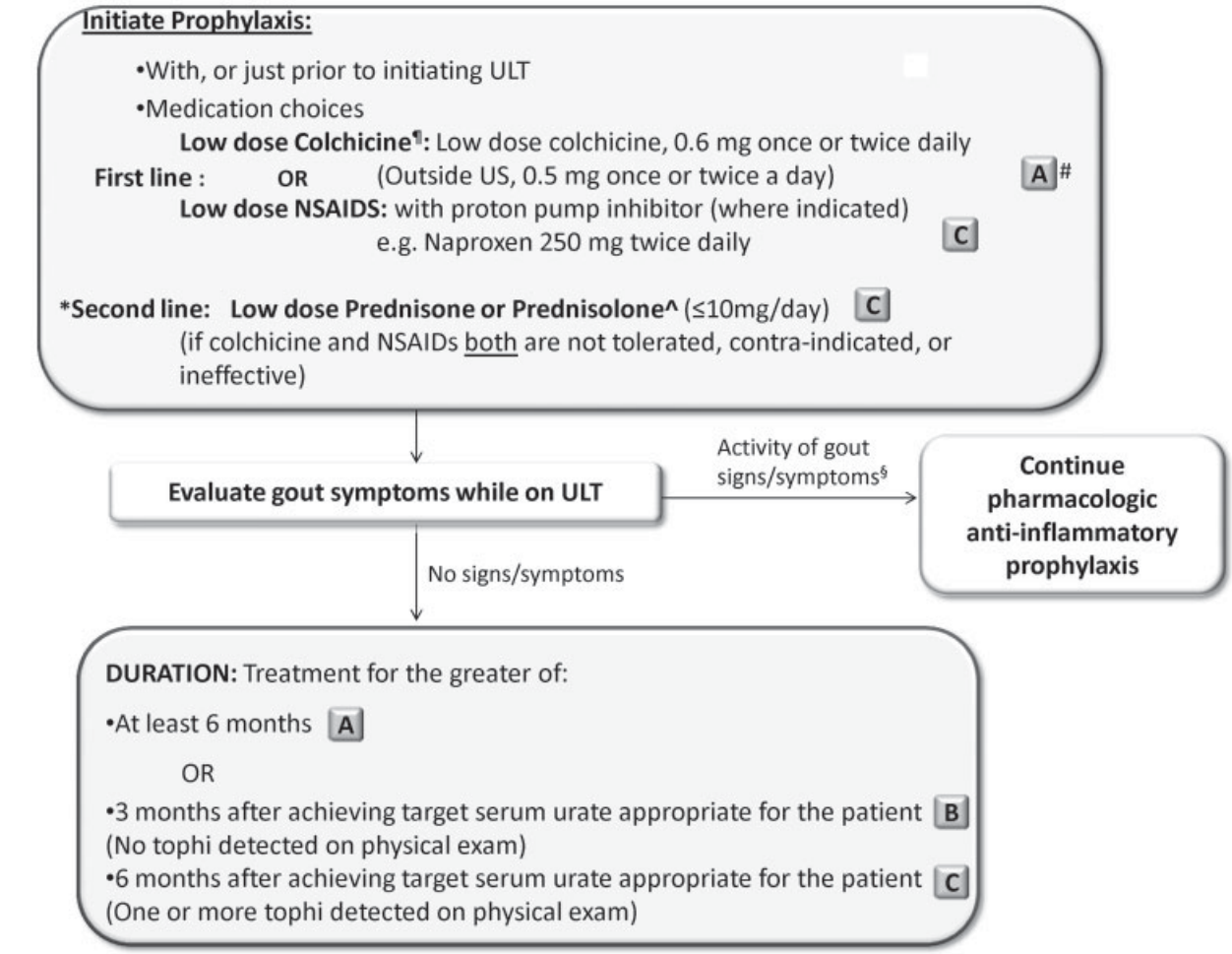
Recommendations for pharmacologic antiinflammatory prophylaxis of attacks of acute gout

The TFP recommended pharmacologic antiinflammatory prophylaxis for all case scenarios of gout where ULT was initiated, given high gout attack rate frequencies in early ULT (evidence A) (51–54) (Figure 5). For gout attack prophylaxis, the TFP recommended, as a first-line option, use of oral colchicine (evidence A) (54,55). The TFP also recommended, as a first-line option (with a lower evidence grade than for colchicine), the use of low-dose NSAIDs (such as naproxen 250 mg orally twice a day), with proton-pump inhibitor therapy or other effective suppression therapy for peptic ulcer disease and its complications, where indicated (evidence C) (54).

In their evaluation of colchicine evidence in gout attack prophylaxis, the TFP specifically recommended low-dose colchicine (0.5 mg or 0.6 mg orally once or twice a day, with dosing further adjusted downward for moderate to severe renal function impairment and potential drug–drug interactions) (30) as appropriate for gout attack prophylaxis. The TFP did not vote on specific quantitative renal function impairment–adjusted dosing of oral colchicine. Since a pharmacokinetic analysis suggesting colchicine dose should be decreased by 50% below a creatinine clearance of 50 ml/minute is unpublished in peer-review form (41), specific quantitative colchicine dose adjustment in CKD is the decision of the treating clinician.

The TFP, in discussion without a specific vote, recognized the evidence that colchicine and low-dose NSAID prophylaxis fail to prevent all gout attacks in patient populations after initiation of ULT (51–54). As an alternative gout attack prophylaxis strategy in patients with intolerance or contraindication or refractoriness to both colchicine and NSAIDs, the TFP recommended use of low-dosage prednisone or prednisolone (defined here as $\leq$10 mg/day) (evidence C). Nevertheless, concerns were raised in discussion among the TFP and by the other authors regarding particularly sparse evidence for efficacy of this low-dose strategy. Given the known risks of prolonged use of corticosteroids, the authors urge clinicians to be particularly attentive in reevaluating the risk/benefit ratio of continued corticosteroid prophylaxis as the risk of acute gout attack decreases with time in conjunction with effective ULT. The TFP voted the use of high daily doses (i.e., $>$10 mg daily) of prednisone or prednisolone for gout attack prophylaxis to be as inappropriate in most case scenarios, and there was a lack of TFP consensus for more severe forms of chronic tophaceous gouty arthropathy. Last, there was a lack of TFP consensus on the risk/benefit ratio for off-label use of biologic IL-1 inhibition (evidence A) (56,57) for antiinflammatory gout attack prophylaxis in patients who previously failed or had intolerance or contraindications to low doses of colchicine, NSAIDs, and prednisone or prednisolone for gout attack prophylaxis.

Duration of antiinflammatory prophylaxis of acute gout attacks. The TFP recommended to continue pharmacologic gout attack prophylaxis if there is any clinical evidence of continuing gout disease activity (such as 1 or


Initiate Prophylaxis:
•With, or just prior to initiating ULT
•Medication choices
Low dose Colchicine¶: Low dose colchicine, 0.6 mg once or twice daily
First line : OR (Outside US, 0.5 mg once or twice a day) A#
Low dose NSAIDS: with proton pump inhibitor (where indicated)
e.g. Naproxen 250 mg twice daily C
*Second line: Low dose Prednisone or Prednisolone^ (≤10mg/day) C
(if colchicine and NSAIDs both are not tolerated, contra-indicated, or ineffective)
Evaluate gout symptoms while on ULT
Activity of gout signs/symptoms§
Continue pharmacologic anti-inflammatory prophylaxis
No signs/symptoms
DURATION: Treatment for the greater of:
•At least 6 months A
OR
•3 months after achieving target serum urate appropriate for the patient B
(No tophi detected on physical exam)
•6 months after achieving target serum urate appropriate for the patient C
(One or more tophi detected on physical exam)

^Without specific task force panel (TFP) vote, the TFP advised that this measure requires particular, continued attention to risk-benefit ratio

§ Examples include: acute gouty arthritis in the past 3 months, presence of palpable tophus or tophi, chronic tophaceous gouty arthropathy (with chronic synovitis) in the past 3 months

**Lack of consensus: Prednisone/prednisolone at doses above 10 mg/day.*

¶ The TFP did not specifically address case scenarios involving renal impairment adjusted colchicine dosing for gout attack prophylaxis

Evidence Grades for Recommendations:
Level A: Supported by multiple (ie, more than one) randomized clinical trials or meta-analyses
Level B: Derived from a single randomized trial, or nonrandomized studies.
Level C: Consensus opinion of experts, case studies, or standard-of-care.

Figure 5. Pharmacologic antiinflammatory prophylaxis of gout attacks and its relationship to pharmacologic urate-lowering therapy (ULT). The figure provides an algorithm for use of antiinflammatory prophylaxis agents to prevent acute gout attacks. The schematic highlights specific recommendations by the TFP on decision making on the initiation, options, and duration of prophylaxis relative to pharmacologic ULT therapy, relative to achievement of the treatment objectives of ULT. NSAIDs = nonsteroidal antiinflammatory drugs.

more tophi detected on physical examination, recent acute gout attacks, or chronic gouty arthritis), and/or the serum urate target has not yet been achieved (1). Specifically, the TFP voted to continue the prophylaxis for the greater of: 1) 6 months' duration (evidence A) (51,53,54), 2) 3 months after achieving the target serum urate level for the patient without tophi detected on physical examination (evidence B), or 3) 6 months after achieving the target serum urate

level, where there has been resolution of tophi previously detected on physical examination (evidence C) (Figure 5).

Discussion

Acute attacks of gout have a detrimental impact on the quality of life of the patient due to pain and dysfunction of affected joints, and acute gout can have a substantial economic and societal impact (58–60). Following a systematic review of the literature and use of a formal group assessment process, we provide the first ACR guidelines for the therapy and antiinflammatory prophylaxis of acute gout attacks.

The TFP recommended multiple modalities (NSAIDs, corticosteroids by different routes, and oral colchicine) as appropriate initial therapeutic options for acute gout attacks. The TFP was informed in part by recent direct comparison studies suggesting approximate equivalency of oral systemic corticosteroids with NSAIDs (28,43). Essentially, the TFP concluded, without a specific vote, that selection of treatment choice is that of the prescribing clinician, and to be based upon factors including patient preference, the patient's previous response to pharmacologic therapies, associated comorbidities and, in the unique case of colchicine, the time since onset of the acute gout attack. The dosing adjustments and relative and absolute contraindications for NSAIDs and colchicine due to associated comorbidities (such as renal and hepatic impairment) and drug interactions were not addressed in these guidelines. There is published literature addressing these issues (30,31) such as quality indicators for safe use of NSAIDs (61–63), including ACR quality indicators for treatment of gout (64).

The TFP recommended a novel set of strict limitations on colchicine doses for acute gout, starting with no more than 1.8 mg over 1 hour in the first 12-hour period of treatment (evidence B) (26), a paradigm shift from widespread prior use of this drug in clinical practice (10,12), but in accordance with FDA guidance. Prior EULAR and BSR recommendations on colchicine dosing for acute gout (10,12) and colchicine low-dose regimen pharmacokinetics (26) informed the TFP recommendation of low-dose colchicine (at a maximum of 0.6 mg twice daily) as a continuation option for an acute gout attack, if started at least 12 hours following the initial low-dose regimen.

For patients with polyarticular joint involvement and severe presentations of gout in 1 or 2 large joints, the TFP recommended, as appropriate, certain first-line combination therapy approaches. Although there is a lack of published randomized controlled trial data to support these recommendations, a large survey of rheumatologists in the US has shown that combination therapy for acute gout is often employed (65).

With respect to antiinflammatory prophylaxis of acute gout attacks, low-dose colchicine or low-dose NSAIDs were recommended as acceptable first-line options by the TFP, with a higher evidence level for colchicine. The use of low-dose colchicine or an NSAID in gout attack prophylaxis is also recommended by EULAR (10). To date, in small clinical trials, low-dose daily oral colchicine was effective in preventing acute gout attacks (3,55), with supportive post hoc analyses in ULT trials (54). The efficacy of low-dose NSAIDs for gout attack prophylaxis also was described in the febuxostat clinical trial program (54); however, prophylaxis was not the primary focus of the trials. Importantly, recent clinical trials of ULT agents have shown substantial rates of acute gout attacks in the first 6 months after the initiation of ULT, even when prophylaxis with colchicine 0.6 mg daily or low-dose NSAID therapy is administered (51–54). It is noteworthy that the TFP recommended prednisone or prednisolone ≤10 mg daily as a second-line option for acute gout prophylaxis, with the caveat that there is a lack of published robust data for the use of low-dose oral prednisone for gout prophylaxis. More investigation is needed to improve management for this clinical problem. Assessment of modulation of cardiovascular event risks by colchicine prophylaxis or by NSAIDs (66) in patients with gout would be particularly informative.

Limitations of the recommendations presented in this article include that only ~30% were based on level A evidence, with approximately half based on level C evidence; this indicates the need for more studies in the aspects of gout management considered here. The process used here was limited by the current trial designs for assessment of acute gout therapies and prophylaxis of antiinflammatory pharmacologic agents in gout. For acute gout studies, most studies were on NSAIDs and involved an active comparator and noninferiority trial design. However, the majority of these studies failed to provide a noninferiority margin, which needs to be defined a priori to assess the validity of these trials. Although the majority of studies assessed pain as the primary outcome for the acute gout trials, there is a lack of a single uniform measure that precludes meta-analysis. Furthermore, there is a lack of consensus on what time period after initiation of therapy constitutes a primary response, since trials ranged from a few hours to 10 days. With the exception of recent analyses of biologic IL-1 inhibitors (56,57), there was a lack of robust clinical trials of gout attack prophylaxis using antiinflammatory pharmacologic agents. Also, the primary measure in these trials is the recurrence of self-reported acute gout attacks, an outcome that has not been validated using Outcome Measures in Rheumatology criteria (67). Efforts are underway to precisely define acute gout attack in gout clinical trials (68). Last, the RAND/UCLA methodology did not address important societal and patient preference issues on treatment costs and cost-effectiveness comparisons between medication choices for acute gout and pharmacologic prophylaxis of acute gout attacks. This is already a pressing question with respect to use of agents, including colchicine and COX-2 selective inhibitors, and would be expected to emerge as a larger issue if biologic IL-1 inhibitors, in late-stage clinical development after phase III studies at the time this was written, obtain regulatory approval for acute gout treatment and prophylaxis.

In summary, these guidelines, the first from the ACR for the management and antiinflammatory prophylaxis of acute attacks of gouty arthritis, have been developed to provide recommendations to clinicians treating patients with gout. The ACR plans to update these guidelines to capture future treatments or advances in the

management and prophylaxis of acute gout, and as the risk/benefit ratios of emerging therapies are further investigated.

Addendum. Therapies that were approved after the original literature review, or diet and lifestyle measures studied after the original literature review, are not included in these recommendations.

ACKNOWLEDGMENTS

We thank Ms Amy Miller and Ms Regina Parker of the ACR for administrative support and guidance. Drs. Jennifer Grossman (UCLA), Michael Weinblatt (Brigham and Women's Hospital, Harvard Medical School), Ken Saag (University of Alabama, Birmingham), and Ted Ganiats (University of California, San Diego) provided valuable guidance on the objectives and process. Rikke Ogawa (UCLA) provided greatly appreciated service as a medical research librarian.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Terkeltaub had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Dinesh Khanna, Puja P. Khanna, Fitzgerald, Manjit K. Singh, Bae, Pillinger, Lee, Prakash, Gogia, Taylor, Choi, Kaplan, Roessler, Kerr, King, Edwards, Mandell, Wenger, Terkeltaub.

Analysis and interpretation of data. Dinesh Khanna, Puja P. Khanna, Fitzgerald, Manjit K. Singh, Bae, Neogi, Merill, Lee, Kaldas, Lioté, Choi, Kaplan, Niyyar, Jones, Yarows, Roessler, Kerr, King, Levy, Furst, Mandell, Schumacher, Robbins, Wenger, Terkeltaub.

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American College of Rheumatology
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Arthritis Care & Research
Vol. 72, No. 6, June 2020, pp 744–760
DOI 10.1002/acr.24180
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ACR GUIDELINE FOR MANAGEMENT OF GOUT

2020 American College of Rheumatology Guideline for the Management of Gout

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Objective. To provide guidance for the management of gout, including indications for and optimal use of urate-lowering therapy (ULT), treatment of gout flares, and lifestyle and other medication recommendations.

Methods. Fifty-seven population, intervention, comparator, and outcomes questions were developed, followed by a systematic literature review, including network meta-analyses with ratings of the available evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, and patient input. A group consensus process was used to compose the final recommendations and grade their strength as strong or conditional.

Results. Forty-two recommendations (including 16 strong recommendations) were generated. Strong recommendations included initiation of ULT for all patients with tophaceous gout, radiographic damage due to gout, or frequent gout flares; allopurinol as the preferred first-line ULT, including for those with moderate-to-severe chronic kidney disease (CKD; stage ≥3); using a low starting dose of allopurinol (≤100 mg/day, and lower in CKD) or febuxostat (≤40 mg/day); and a treat-to-target management strategy with ULT dose titration guided by serial serum urate (SU) measurements, with an SU target of <6 mg/dl. When initiating ULT, concomitant antiinflammatory prophylaxis therapy for a duration of at least 3–6 months was strongly recommended. For management of gout flares, colchicine, nonsteroidal antiinflammatory drugs, or glucocorticoids (oral, intraarticular, or intramuscular) were strongly recommended.

Conclusion. Using GRADE methodology and informed by a consensus process based on evidence from the current literature and patient preferences, this guideline provides direction for clinicians and patients making decisions on the management of gout.

This article is published simultaneously in *Arthritis & Rheumatology*.
Supported by the American College of Rheumatology.
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INTRODUCTION

Gout is the most common form of inflammatory arthritis, affecting ~9.2 million adults (3.9%) in the US (1). While the etiology of gout is well-understood and there are effective and inexpensive medications to treat gout, gaps in quality of care persist (2–4). The 2012 American College of Rheumatology (ACR) Guidelines for the Management of Gout (5,6) and other international specialty society guidelines recommend treat-to-target strategies with use of urate-lowering therapy (ULT) (7–10). Despite these recommendations, over the past 2 decades there has been no increase in ULT utilization. Adherence to ULT remains poor (2,11) and is the lowest adherence among treatments for 7 common chronic medical conditions (12). Complicating the efforts to improve adherence is the fact that the prior 2012 ACR Guidelines for the Management of Gout have been criticized due to low quality of evidence supporting treat-to-target recommendations (13,14). Since the 2012 ACR Guidelines for the Management of Gout were published, several clinical trials have been conducted that provide additional evidence regarding the management of gout, leading the ACR Guidelines Subcommittee to determine that new guidelines were warranted.

METHODS

This guideline follows the ACR guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the certainty of evidence and develop recommendations (15–17), with an emphasis on developing actionable guidelines. ACR policy guided the management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Gout). A full description of the methods is presented in Supplementary Appendix 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract).

Briefly, the Core Team, Expert Panel, and Voting Panel (consisting of rheumatologists, a general internist, a nephrologist, a physician assistant, and a patient representative) generated 57 population, intervention, comparator, and outcomes (PICO) questions to address the following: indications for ULT (5 questions), approaches to initiating ULT (7 questions), ongoing ULT management (18 questions), gout flares (10 questions), and lifestyle and other medication strategies in patients with gout (9 questions) and in individuals with asymptomatic hyperuricemia (8 questions). PICO questions were posted on the ACR web site for public comment (October 30–November 30, 2018) (for a list of team and panel members, see Supplementary Appendix 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract). An in-person Patient Panel of 8 male patients with gout, moderated by one of the voting panel members (JAS), reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives and preferences.

The Core Team prespecified outcomes as critical or important for each PICO question for the systematic literature review. Outcomes varied across PICO topic (for details, see Supplementary Appendix 3, at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract). Gout flare and serum urate (SU) concentration (and tophus for PICO question 1) were specified as critical outcomes for all PICO questions specific to ULT. Pain was identified as critical for PICO questions specific

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Dr. FitzGerald holds a patent for a lens-free microscope. Dr. Dalbeth has received consulting fees, speaking fees, and/or honoraria from Janssen, AbbVie, Dyve Biosciences, Arthrosi Therapeutics, Horizon, AstraZeneca, and Hengrui (less than $10,000 each). Dr. Mikuls has received consulting fees from Pfizer (less than $10,000) and research support from Horizon Therapeutics and Bristol-Myers Squibb. Dr. Harrold owns stock or stock options in Corrona. Dr. D. Khanna has received consulting fees, speaking fees, and/or honoraria from Horizon (less than $10,000) and owns stock or stock options in Eicos Sciences. Dr. Mount has received consulting fees from Horizon Pharma (less than $10,000). Dr. Pillinger has received research support from Hikma Pharmaceuticals and Horizon Pharma. Dr. Singh has received consulting fees, speaking fees, and/or honoraria from Crealta/Horizon, Medisys, Fidia, UBM, Trio Health, Medscape, WebMD, Clinical Care Options, Clearview Healthcare Partners, Putnam Associates, Spherix, and Practice Point Communications (less than $10,000 each) and owns stock or stock options in Amarin Pharmaceuticals and Viking Therapeutics. Dr. P. Khanna has received research support from Ironwood and Sobi. No other disclosures relevant to this article were reported.

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Submitted for publication December 10, 2019; accepted in revised form February 28, 2020.

to gout flare. Gout flare was specified as the only critical outcome for management of lifestyle factors. All other outcomes were specified as important. Without standardized definitions for gout flare as an outcome (18), flare definitions varied by duration of follow-up in the various studies. Based on Patient Panel input, we specified that longer-term outcomes (e.g., 24 months) would be critical, while shorter durations (e.g., ≤12 months) were considered important; it was recognized that very short time points (e.g., <6 months) may reflect the expected flares during ULT initiation.

We conducted systematic literature reviews (including 2 network meta-analyses [NMAs]) to address each PICO question (for search strategies and study selection process, see Supplementary Appendices 4 and 5, respectively, at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract). The first NMA evaluated the impact of starting ULT versus no ULT and the relative impact of the various ULT agents (for details, see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract). The second NMA evaluated antiinflammatory agents in gout flare management (for details, see Supplementary Appendix 7, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract). To accomplish this second NMA, we grouped similar agents into nodes (e.g., acetic acid derivatives, profens, cyclooxygenase 2 agents, glucocorticoids, and interleukin-1 [IL-1] inhibitors).

The lowest level of evidence for the outcomes deemed critical to patients determined the certainty of evidence for each PICO question (15). For PICO questions specific to ULT, and on the basis of input from 1) the Patient Panel; 2) prior focus group work citing the importance of SU, gout flare, and tophi to patients (19); and 3) prior guidance from the GRADE working group (20), we made the following decisions. Where there was moderate or high certainty of evidence demonstrating improvement in any 1 of these 3 outcomes, we deemed this sufficient evidence to support a strong recommendation. The certainty of evidence from the other 2 outcomes was then designated as important but not critical to support the recommendation. The certainty of the evidence for each recommendation is presented in Tables 1–8, and the certainty of evidence for each outcome within each PICO question is in the full evidence report (see Supplementary Appendix 8, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract).

Additionally, we report results using the more conservative rating of the evidence using the lowest level of evidence for any of the critical outcomes. Applying these more conservative rules, the summary certainty of evidence decreased (in comparison to the reported results) for some of the ULT recommendation statements, which would result in a lower strength of recommendation for 2 recommendations (PICO question 2: ULT indication for patients with erosions, and PICO question 27: switching to pegloticase for ULT failure). The details are available in the evidence report (Supplementary Appendix 8). Medication costs (not part of the systematic literature review), reported as average wholesale pricing as sourced from Lexicomp on August 23, 2019, were provided to the Voting Panel, as cost of treatment was included as part of the evaluation of risks and benefits of treatment medications (see Supplementary Appendix 9, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract).

PICO questions were drafted into recommendation statements and were sent to the Voting Panel with the evidence report prior to round 1 voting. At a face-to-face meeting, the Voting Panel again reviewed draft recommendations, a summary of the voting results from round 1, the evidence report, and a summary of Patient Panel statements (1 patient from the Patient Panel [JES] and the Patient Panel moderator [JAS] attended the Voting Panel and were available to answer questions about the Patient Panel statements). To become a recommendation (for or against) in this guideline, at least 70% consensus of the Voting Panel was required.

The strength of each recommendation was rated as *strong* or *conditional. Strong* recommendations reflect decisions supported by moderate or high certainty of evidence where the benefits consistently outweigh the risks, and, with only rare exceptions, an informed patient and his or her provider would be expected to reach the same decision. *Conditional* recommendations reflect scenarios for which the benefits and risks may be more closely balanced and/or only low certainty of evidence or no data are available.

Recommendations in this guideline apply to patients with gout, except for a single recommendation regarding the use of ULT in individuals with asymptomatic hyperuricemia, which is defined as an SU concentration of ≥6.8 mg/dl with no prior gout flares or subcutaneous tophi. Patients with evidence of monosodium urate monohydrate (MSU) deposition on advanced imaging may still be considered asymptomatic if they have not had a prior gout flare or subcutaneous tophi.

These guidelines do not directly address the impact of gout or hyperuricemia on other comorbidities, such as cardiovascular disease (CVD), hypertension, urolithiasis, or chronic kidney disease (CKD). As we developed these guidelines for use by providers practicing in the US, we considered pharmacologic therapies available in the US, with select exceptions. Although lesinurad was withdrawn from the US market by the manufacturer during the course of guideline development, it remains Food and Drug Administration (FDA) approved, and we therefore considered the data in relation to relevant PICO questions. To facilitate the 2 NMAs, we also considered medications not available in the US to permit comparisons with other available medications in the network analysis.

RESULTS/RECOMMENDATIONS

Indications for pharmacologic ULT

Initiating ULT is strongly recommended for gout patients with any of the following: ≥1 subcutaneous tophi; evidence of radiographic damage (any modality) attributable to gout; OR frequent gout flares, with frequent being defined as ≥2 annually.

From the ULT NMA (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract) and randomized clinical trials (RCTs) of pegloticase (21–23) and lesinurad (24), there was high certainty of evidence regarding the efficacy of ULT in reducing flare frequency (23–26), tophi (21,23), and SU concentrations (23–26). While many Patient Panel participants reported that they were initially hesitant to start ULT, after experiencing improved control of inflammatory symptoms and tophi, they became strong advocates for its earlier institution (for all indications for pharmacologic ULT, see Table 1 and Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract).

Initiating ULT is conditionally recommended for patients who have previously experienced >1 flare but have infrequent flares (<2/year).

For patients with less frequent flares and no tophi, the potential clinical benefit of ULT would be lower than the ULT benefit for patients with more burdensome gout. In a single study (moderate certainty of evidence), patients with ≤2 previous flares (and no more than 1 gout flare in the preceding year) randomized to receive febuxostat (versus placebo) were less likely to experience a subsequent flare (30% versus 41%; $P < 0.05$) (27).

Specific characteristics for patients with infrequent flares (e.g., SU concentration >9 mg/dl, CKD, CVD) that might influence the risk-benefit assessment were considered, but due to insufficient data for these subgroups, the Voting Panel did not find that these conditions warranted stronger ULT recommendations specific to these subgroups.

Initiating ULT is conditionally recommended *against* in patients with gout experiencing their first gout flare.

However, initiating ULT is conditionally recommended for patients with comorbid moderate-to-severe CKD (stage ≥3), SU concentration >9 mg/dl, or urolithiasis.

While conditionally recommending *against* ULT initiation following the first gout flare in a patient with "uncomplicated" gout, the Voting Panel considered Patient Panel input and recognized that there may be patients who would prefer (or benefit from) ULT, underscoring the need for shared decision-making. As noted above, data from the RCT of patients with ≤2 previous flares (and no more than 1 gout flare in the preceding year) supported the benefit of ULT for reduction of SU concentration and gout flare risk (27). For patients with moderate-to-severe CKD (e.g., stage ≥3), there is a higher likelihood of gout progression and development of clinical tophi (28–30). Furthermore, treatment options for gout flare are limited in this population, and there may be added benefit of using ULT to prevent progression of renal disease (31). Similarly, patients with markedly elevated SU concentrations (>9 mg/dl) are more likely to experience gout progression (26,32). For patients with a history of urolithiasis, allopurinol and febuxostat provide benefit, as both medications lower 24-hour urinary uric acid excretion more than placebo (33). Among patients with calcium oxalate stones and hyperuricosuria, allopurinol (300 mg/day) is superior to placebo in reducing the 3-year incidence of stone-related events (34).

Table 1. Indications for pharmacologic urate-lowering therapy (ULT)*

Recommendation	PICO question	Certainty of evidence
For patients with 1 or more subcutaneous tophi, we strongly recommend initiating ULT over no ULT.	1	High
For patients with radiographic damage (any modality) attributable to gout, we strongly recommend initiating ULT over no ULT.	2	Moderate
For patients with frequent gout flares (≥2/year), we strongly recommend initiating ULT over no ULT.	3	High
For patients who have previously experienced >1 flare but have infrequent flares (<2/year), we conditionally recommend initiating ULT over no ULT.	4	Moderate
For patients experiencing their first flare, we conditionally recommend *against* initiating ULT over no ULT, with the following exceptions.	5	Moderate
For patients experiencing their first flare and CKD stage ≥3, SU >9 mg/dl, or urolithiasis, we conditionally recommend initiating ULT.	5	Very low
For patients with asymptomatic hyperuricemia (SU >6.8 mg/dl with no prior gout flares or subcutaneous tophi), we conditionally recommend *against* initiating any pharmacologic ULT (allopurinol, febuxostat, probenecid) over initiation of pharmacologic ULT.	57	High†

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; CKD = chronic kidney disease; SU = serum urate.
† There is randomized clinical trial data to support the benefit that ULT lowers the proportion of patients who develop incident gout. However, based on the attributable risk, 24 patients would need to be treated for 3 years to prevent a single (incident) gout flare leading to the recommendation against initiating ULT in this patient group.

Initiating ULT is conditionally recommended *against* in patients with asymptomatic hyperuricemia.

For patients with asymptomatic hyperuricemia, RCTs (designed to study CVD outcomes) demonstrated significant reduction in incident gout flares over 3 years. However, the development of incident gout was low for both ULT and placebo arms (<1% versus 5%) (35,36). In other words, 24 patients would need to be treated with ULT for 3 years to prevent a single (incident) gout flare. From observational studies, among patients with asymptomatic hyperuricemia with SU concentrations of >9 mg/dl, only 20% went on to develop gout within 5 years (32). The Voting Panel felt that, on average, for the majority of patients with asymptomatic hyperuricemia (including those with comorbid CKD, CVD, urolithiasis, or hypertension), the benefits of ULT would not outweigh potential treatment costs or risks for the large number of patients unlikely to progress to gout. This is also the case for patients with asymptomatic hyperuricemia with MSU crystal deposition as noted on imaging tests such as ultrasound or dual-energy computed tomography.

Recommendations for choice of initial ULT for patients with gout

Treatment with allopurinol as the preferred first-line agent, over all other ULTs, is strongly recommended for all patients, including those with moderate-to-severe CKD (stage ≥3).

The Voting Panel strongly recommended allopurinol as the preferred first-line agent given its efficacy when dosed appropriately (often required doses >300 mg/day [37] up to the maximum FDA-approved dose of 800 mg/day [38]), tolerability, safety, and lower cost. Using a lower starting dose mitigates safety issues specific to allopurinol hypersensitivity syndrome (AHS) (39,40). The Voting Panel indicated that an optimal trial of oral medication would be appropriate prior to pegloticase due to cost differences and potential adverse effects of the latter medication (for recommendations for choice of initial ULT, see Table 2 and Supplementary Figure 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract).

The choice of either allopurinol or febuxostat over probenecid is strongly recommended for patients with moderate-to-severe CKD (stage ≥3).

The choice of pegloticase as a first-line therapy is strongly recommended *against*.

Starting treatment with low-dose allopurinol (≤100 mg/day and lower in patients with CKD [stage ≥3]) and febuxostat (≤40 mg/day) with subsequent dose titration over starting at a higher dose is strongly recommended.

Starting treatment with low-dose probenecid (500 mg once to twice daily) with subsequent dose titration over starting at a higher dose is conditionally recommended.

A lower starting dose of any ULT reduces the risk of flare associated with initiation (41). The Patient Panel voiced a strong preference for safer ULT prescribing regimens through lower starting doses with subsequent dose escalation, even if such regimens required more blood draws and provider visits, over alternate regimens (e.g., starting with higher doses) that might incur more risk. Even lower initial allopurinol doses (e.g., ≤50 mg/day)

Table 2. Recommendations for choice of initial urate-lowering therapy (ULT) in patients with gout*

Recommendation	PICO question	Certainty of evidence
For patients starting any ULT, we strongly recommend allopurinol over all other ULT as the preferred first-line agent for all patients, including in those with CKD stage ≥3.	10	Moderate
We strongly recommend a xanthine oxidase inhibitor over probenecid for those with CKD stage ≥3.		
For allopurinol and febuxostat, we strongly recommend starting at a low dose with subsequent dose titration to target over starting at a higher dose (e.g., ≤100 mg/day [and lower in patients with CKD] for allopurinol or ≤40 mg/day for febuxostat).	7	Moderate
For probenecid, we conditionally recommend starting at a low dose (500 mg once or twice daily) with dose titration over starting at a higher dose.		
We strongly recommend initiating concomitant antiinflammatory prophylaxis therapy (e.g., colchicine, NSAIDs, prednisone/prednisolone) over no antiinflammatory prophylaxis. The choice of specific antiinflammatory prophylaxis should be based upon patient factors.	9	Moderate
We strongly recommend continuing prophylaxis for 3–6 months rather than <3 months, with ongoing evaluation and continued prophylaxis as needed if the patient continues to experience flares.	9	Moderate
When the decision is made that ULT is indicated while the patient is experiencing a gout flare, we conditionally recommend starting ULT during the gout flare over starting ULT after the gout flare has resolved.	6	Moderate
We strongly recommend *against* pegloticase as first-line therapy.	10	Moderate†

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; CKD = chronic kidney disease; NSAIDs = nonsteroidal antiinflammatory drugs.
† Moderate evidence is in support of the efficacy of pegloticase, but due to cost, safety concerns, and favorable benefit-to-harm ratios of other untried treatment options, the recommendation is *against* using pegloticase as first-line agent.

should be considered in patients with CKD. While higher starting doses and CKD are associated with risk of AHS (39), patients with CKD may still require dose titration above 300 mg/day to achieve the SU target (42,43). A population pharmacokinetic–pharmacodynamics study showed that larger body size and diuretic use indicated the need for higher allopurinol doses to achieve greater urate reduction. Worse renal function only had a modest negative impact on urate reduction (44). Other studies have demonstrated that allopurinol dose escalation can be done safely in this population (40,45).

Administering concomitant antiinflammatory prophylaxis therapy (e.g., colchicine, nonsteroidal antiinflammatory drugs [NSAIDs], prednisone/prednisolone) over no antiinflammatory prophylaxis therapy is strongly recommended.

Based on 8 RCTs (41,46–52) and 2 observational studies (53,54), there is moderate certainty of evidence to support the strong recommendations to use antiinflammatory prophylaxis therapy when initiating ULT. Continuation of prophylaxis for at least 3–6 months after ULT initiation was recommended because shorter durations were associated with flares upon cessation of prophylaxis (55,56). After cessation, monitoring for flare activity and continuation of antiinflammatory treatment as needed if the patient continues to experience flares was recommended.

Continuing concomitant antiinflammatory prophylaxis therapy for 3–6 months over <3 months, with ongoing evaluation and continued prophylaxis as needed if the patient continues to experience gout flares, is strongly recommended.

Timing of ULT initiation

When the decision is made that ULT is indicated while the patient is experiencing a gout flare, starting ULT during the gout flare over starting ULT after the gout flare has resolved is conditionally recommended.

Starting ULT during a flare has conceptual benefits, including the time efficiency offered by initiating therapy during the concurrent flare visit rather than risking the patient not returning for ULT initiation. Furthermore, input from the Patient Panel emphasized that patients are likely to be highly motivated to take ULT due to the symptoms related to the current flare. However, concerns about starting ULT during a flare include potential extension or worsening of a flare, as well as the possibility of information overload for patients, which may lead to conflating flare management and long-term ULT. Two small RCTs (57,58) and an observational study (59) support the hypothesis that starting ULT during a flare does not significantly extend flare duration or severity. Input from the Patient Panel, citing their own ability to simultaneously process information related to flare treatment and ULT initiation together, along with their preference to start on a treatment path sooner to prevent future flares, influenced the final recommendation. As with all conditional recommendations, there may be patient factors or preferences that would reasonably support the alternative of delaying ULT initiation until the flare has resolved.

A treat-to-target management strategy that includes ULT dose titration and subsequent dosing guided by serial SU measurements to achieve a target SU, over a fixed-dose ULT strategy, is strongly recommended for all patients receiving ULT.

Achieving and maintaining an SU target of <6 mg/dl over the use of no target is strongly recommended for all patients receiving ULT.

We recommend using a treat-to-target management strategy to optimize patient outcomes by achieving and maintaining an SU target of <6 mg/dl rather than using a fixed-dose strategy (Table 3 and Supplementary Figure 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract). There is moderate- and high-quality evidence supporting these 2 recommendations. In an RCT from the UK (43), patients randomized to a nurse-led, treat-to-target protocol demonstrated greater ULT adherence, lower SU concentrations, reduction in tophi, and a lower proportion of frequent (≥2) gout flares at 24 months, compared with patients randomized to general practitioner–led usual care (an approach more often characterized by a fixed-dose strategy when ULT is administered). Two separate pharmacist-led interventions in the US, both incorporating treat-to-target strategies, were superior to usual care in terms of treatment adherence, SU outcomes, and higher allopurinol dosing (60,61). Additional studies provide support for ULT dose escalation to achieve target SU levels, including dose titration of allopurinol in patients with CKD (40,43). While a specific dose titration schedule is left to provider and patient to individualize based on patient comorbidities and preferences, ULT titration should occur over a reasonable time frame (e.g., weeks to months, not years) to prevent "treatment inertia" (62). In contrast to the 2012 ACR Guidelines for the Management of Gout, due to lack of supporting evidence for additional specific thresholds, we do not define further thresholds for patients warranting more intensive ULT.

Delivery of an augmented protocol of ULT dose management by nonphysician providers to optimize the treat-to-target strategy that includes patient education, shared decision-making, and treat-to-target protocol is conditionally recommended for all patients receiving ULT.

Based on recent nurse- (43) and pharmacist-led (60,61) interventions, the Voting Panel supported the benefit of an augmented delivery-of-care using patient education and shared decision-making through implementation of a treat-to-target protocol over

Table 3. Recommendations for all patients taking urate-lowering therapy (ULT)*

Recommendation	PICO question	Certainty of evidence
For all patients taking ULT, we strongly recommend a treat-to-target strategy of ULT dose management that includes dose titration and subsequent dosing guided by serial SU values to achieve an SU target over a fixed, standard-dose ULT strategy.	13	Moderate
For all patients taking ULT, we strongly recommend continuing ULT to achieve and maintain an SU target of <6 mg/dl over no target.	14	High
For all patients taking ULT, we conditionally recommend delivery of an augmented protocol of ULT dose management by nonphysician providers to optimize the treat-to-target strategy that includes patient education, shared decision-making, and treat-to-target protocol.	8	Moderate
We conditionally recommend continuing ULT indefinitely over stopping ULT.	19	Very low

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; SU = serum urate.

usual care. However, the panel recognized that these resources may not be available in all health care settings, and that the key is for the treating provider (who could be the treating physician) to educate the patient and implement a treat-to-target protocol.

Duration of ULT

Continuing ULT indefinitely over stopping ULT is conditionally recommended.

For patients in clinical remission taking ULT (e.g., no flares for ≥1 year and no tophi [63]), the Voting Panel considered ULT cessation or tapering. In a single case series where ULT was withheld in patients in clinical remission with years of well-controlled SU concentrations prior to cessation, only 13% of patients (27 of 211) whose SU concentration remained at <7 mg/dl while not receiving ULT had no flares during a 5-year follow-up period. Furthermore, patients with higher SU concentrations after withholding therapy had more frequent flares with greater likelihood of flares associated with higher SU levels (37). The Patient Panel voiced concerns about a return or worsening of gout symptoms, tophi, or joint damage with ULT cessation. If therapy is well-tolerated and not burdensome, the Patient Panel expressed a preference to continue treatment.

Recommendations for patients receiving ULT medications

Allopurinol

Testing for the HLA–B*5801 allele prior to starting allopurinol is conditionally recommended for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and for African American patients, over not testing for the HLA–B*5801 allele.

Universal testing for the HLA–B*5801 allele prior to starting allopurinol is conditionally recommended *against* in patients of other ethnic or racial background over testing for the HLA–B*5801 allele.

As noted above, starting allopurinol in daily doses of ≤100 mg (and lower doses in patients with CKD) is strongly recommended over starting at a higher dose.

The HLA–B*5801 allele is associated with a markedly elevated risk for AHS (64,65). The prevalence of HLA–B*5801 is highest among persons of Han Chinese, Korean, and Thai

Table 4. Recommendations for patients taking specific urate-lowering therapy (ULT) medications*

Recommendation	PICO question	Certainty of evidence
Allopurinol		
We conditionally recommend testing HLA–B*5801 prior to starting allopurinol for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and African American patients, who have a higher prevalence of HLA–B*5801.	12	Very low
We conditionally recommend *against* HLA–B*5801 testing in all others.		
For patients with a prior allergic response to allopurinol who cannot be treated with other oral ULT, we conditionally recommend using allopurinol desensitization.	23	Very low
Febuxostat		
For patients with gout taking febuxostat with a history of CVD or a new CV event, we conditionally recommend switching to an alternative ULT agent if available and consistent with other recommendations in this guideline.	22	Moderate
Uricosurics		
For patients considered for, or taking uricosuric treatment, prior to starting any uricosuric treatment, we conditionally recommend *against* checking urinary uric acid over checking urinary uric acid.	28	Very low
For patients taking uricosuric treatment, we conditionally recommend *against* alkalinizing urine.	29	Very low

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; CVD = cardiovascular disease.

descent (7.4%) (66), lower among African Americans (3.8%), and even lower among whites and Hispanics (0.7% each) (66). Testing for this allele among Asians and African American patients was reported to be cost-effective (incremental cost-effectiveness ratios <$109,000 per quality-adjusted life years) (67). Asian and African American patients taking allopurinol both have a 3-fold increased risk of AHS compared with white patients taking allopurinol (68) (for recommendations for ULT medications, see Table 4 and Supplementary Figure 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract).

Allopurinol desensitization is conditionally recommended for patients with a prior allergic response to allopurinol who cannot be treated with other oral ULT agents.

The level of evidence supporting this recommendation was very low (69,70). The Voting Panel recognized that desensitization protocols (69,70) are not commonly used, with the majority of currently practicing rheumatologists having limited experience in these protocols.

Febuxostat

Switching to an alternative oral ULT agent, if available and consistent with other recommendations in this guideline, is conditionally recommended for patients taking febuxostat with a history of CVD or a new CVD-related event.

At the Voting Panel meeting, there was much discussion about the data, Patient Panel input, and interest to provide recommendations consistent with the FDA black box warning for febuxostat (71). The Voting Panel considered data from the CARES RCT (72) and 2 observational studies (73,74). In the FDA-mandated CARES trial of febuxostat versus allopurinol (72), there was no difference between the 2 arms in the primary composite CVD end point. Febuxostat, however, was associated with a higher risk of CVD-related death and all-cause mortality (driven by CVD deaths) compared with allopurinol, but there was no association with the other 3 secondary CVD outcomes (nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization for unstable angina). Interpretation of these results is complicated by a high dropout rate with a majority of deaths occurring after ULT discontinuation (72). Moreover, the lack of an untreated control group means the absolute CVD risk related to febuxostat is unknown. A large observational study (recruitment not selected for CVD) did not show an increased risk of CVD or all-cause mortality associated with febuxostat initiation compared with allopurinol using methods to address confounding by indication (73). Another study using a managed care database demonstrated lower risk of any major CVD event among febuxostat initiators than allopurinol initiators, though confounding by indication may not have been adequately addressed (74). The Patient Panel representative stated members would be willing to accept "some" incremental CVD risk as long as the treatment adequately controlled their gout. Thus, as for many such decisions with conditional recommendations, providers and patients should engage in shared decision-making when considering febuxostat for patients at high risk for CVD.

Uricosurics

Checking urinary uric acid is conditionally recommend *against* for patients considered for or receiving uricosuric treatment.

Alkalinizing the urine is conditionally recommended *against* for patients receiving uricosuric treatment.

A single observational study demonstrated that higher levels of 24-hour urinary uric acid and higher levels of undissociated urinary uric acid were associated with urolithiasis (75). However, the Voting Panel indicated that the challenges with 24-hour urine collection or nomogram-based testing, which can both be affected by diet, negate the utility of such testing in light of a very low level of evidence.

We found no evidence to support a recommendation of checking urinary uric acid level for patients receiving uricosuric treatment or for alkalinizing the urine. The Voting Panel supported standard best practice that patients with known renal calculi or moderate-to-severe CKD (stage $\geq$3) should not be treated with uricosurics. For patients who are treated with uricosurics, patients should receive counseling about adequate hydration, but they need not be prescribed alkalinizing agents given the lack of evidence for efficacy.

As use of uricosurics remains infrequent, we did not formally vote on indications for uricosuric medications. However, we concur with the 2012 ACR Guidelines for the Management of Gout that add-on therapy to partially responsive xanthine oxidase inhibitor (XOI) treatment can result in improved SU control (24,25,76).

When to consider changing ULT strategy

Switching to a second XOI over adding a uricosuric agent is conditionally recommended for patients taking their first XOI, who have persistently high SU concentrations (>6 mg/dl) despite maximum-tolerated or FDA-indicated XOI dose, and who have continued frequent gout flares (>2 flares/year) OR who have nonresolving subcutaneous tophi.

Several lesinurad studies demonstrated the benefit of adding a uricosuric medication to XOI treatment (25,76). However, we found no studies directly addressing the choice in the above

PICO question, resulting in the conditional recommendation to switch to a second XOI after the first XOI failure (for recommendations for consideration of changing ULT strategy, see Table 5 and Supplementary Figure 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract).

Switching to pegloticase over continuing current ULT is strongly recommended for patients with gout for whom XOI treatment, uricosurics, and other interventions have failed to achieve the SU target, and who continue to have frequent gout flares (≥2 flares/year) OR who have nonresolving subcutaneous tophi.

Switching to pegloticase over continuing current ULT is strongly recommended *against* for patients with gout for whom XOI treatment, uricosurics, and other interventions have failed to achieve the SU target, but who have infrequent gout flares (<2 flares/year) AND no tophi.

In clinical trials, patients with 3 or more self-reported gout flares during the previous 18 months, ≥1 tophi, and gouty arthropathy, defined clinically or radiographically as joint damage due to gout, were randomly assigned to pegloticase treatment. Patients additionally had contraindication to treatment with allopurinol or history of treatment failure to normalize uric acid despite ≥3 months of treatment with the maximum medically appropriate allopurinol dose (determined by the treating physician). For these patients with frequent gout flares or nonresolving subcutaneous tophi, clinical trials demonstrated improved SU concentrations, low frequency of flares (77), reduction in tophi (21), and improved quality of life (22) among those receiving pegloticase. However, these outcomes come with high costs, twice-monthly infusions, and the potential for serious allergic reactions. For patients with infrequent gout flares and no tophi, we would expect a similar benefit in SU reduction. For patients with only infrequent flares, the magnitude of benefit would be substantially smaller than for patients with frequent flares, and there would be no benefit in reduction of tophi when no tophi are present. The harms and costs of administering pegloticase would likely be similar in patients with mild versus severe disease, resulting in limited benefit and appreciable harm along with very high costs, leading the panel to conclude that the costs and harms clearly outweigh the benefits. This conclusion, along with strong Patient Panel statements about not wanting to receive twice-monthly infusions to prevent infrequent gout flares, resulted in the strong recommendation *against* using pegloticase for patients with mild disease.

The above scenarios represent extremes of gout clinical severity resulting in strong "for" and "against" recommendations. The Voting Panel considered intermediary scenarios, but given the potential variability, the panel opted to simply defer to provider judgment balanced with patient preferences, regarding the optimal treatment strategy for individuals not described above. To clarify, as outlined above, there is a strong recommendation to follow a treat-to-target management strategy for all patients receiving ULT. However, the recommendation for treat-to-target strategy is not absolute and not meant to be pursued at "any cost." Even strong recommendations require sound clinical judgment to balance the potential clinical benefits and harms (including costs) of medical decisions (78).

Gout flare management

Using colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or adrenocorticotropic hormone (ACTH) is strongly recommended for patients experiencing a gout flare.

Given similar efficacy and a lower risk of adverse effects, low-dose colchicine over high-dose colchicine is strongly recommended when colchicine is the chosen agent.

Table 5. When to consider switching to a new urate-lowering therapy (ULT) strategy*

Recommendation	PICO question	Certainty of evidence
For patients with gout taking their first XOI monotherapy at maximum-tolerated or FDA-indicated dose who are not at SU target and/or have continued frequent gout flares or nonresolving subcutaneous tophi, we conditionally recommend switching the first XOI to an alternate XOI agent over adding a uricosuric agent.	24	Very low
For patients with gout where XOI, uricosurics, and other interventions have failed to achieve SU target and who have frequent gout flares or nonresolving subcutaneous tophi, we strongly recommend switching to pegloticase over continuing current ULT.†	27	Moderate
For patients with gout for whom XOI, uricosurics, and other interventions have failed to achieve serum urate target and who have infrequent gout flares (<2 flares/year) and no tophi, we strongly recommend *against* switching to pegloticase over continuing current ULT.‡	27	Moderate

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; XOI = xanthine oxidase inhibitor; FDA = Food and Drug Administration.
† There is moderate certainty of evidence about the efficacy of the benefits, harms, and high certainty about the costs of pegloticase. For patients with high disease activity, the magnitude of potential benefits outweighs the harms and costs of the drug.
‡ For patients with minimal disease activity, the smaller potential benefits do not outweigh the harms and costs of the drug.

Using topical ice as an adjuvant treatment over no adjuvant treatment is conditionally recommended for patients experiencing a gout flare.

Using an IL-1 inhibitor over no therapy (beyond supportive/analgesic treatment) is conditionally recommended for patients experiencing a gout flare for whom the above antiinflammatory therapies are either ineffective, poorly tolerated, or contraindicated.

Treatment with glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH is strongly recommended for patients who are unable to take oral medications.

The Voting Panel's recommendation of colchicine, NSAIDs, or glucocorticoids as preferred first-line therapies was based on substantial trial data demonstrating efficacy, relative low cost (versus IL-1 inhibitors and ACTH), and tolerability of these agents in flare management, particularly when administered early after symptom onset. Appropriate dosing and duration should be guided by the severity of the flare. For colchicine specifically, the FDA-approved dosing should be followed (1.2 mg immediately followed by 0.6 mg an hour later, with ongoing antiinflammatory therapy until the flare resolves). Based on similar efficacy between agents demonstrated in the NMA (79–88), the Voting Panel did not further prioritize between the first-line agents, noting that treatment selection should be driven by patient factors (e.g., comorbidity, access, past experience) as part of shared decision-making. Likewise, parenteral glucocorticoids were favored over alternative agents when oral dosing is not possible. In patients experiencing an inadequate response to an initial agent, the Voting Panel cited insufficient evidence to make specific recommendations regarding subsequent antiinflammatory agents to use. If a patient is unable to tolerate or has contraindications to any of the other conventional alternatives, the Voting Panel conditionally recommended the use of IL-1 inhibitors (84,88–90), recognizing concerns over patient access due to cost. Noting limited supporting data (91), the Voting Panel recommended the use of topical ice as an adjuvant therapy for flares.

Underscoring the importance of optimal flare management, the Patient Panel emphasized its preference for early intervention given the challenges of engaging a provider in timely manner, including an at-home "medication-in-pocket" strategy for patients who are able to identify the early signs of flare onset. In the absence of "rapid" access to an effective oral medication, the Patient Panel also indicated its preference for an injectable therapy in appropriate circumstances to achieve pain relief as quickly as possible (for all recommendations for gout flare managment, see Table 6 and Supplementary Figure 4, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract).

Management of lifestyle factors

Limiting alcohol intake is conditionally recommended for patients with gout, regardless of disease activity.

Limiting purine intake is conditionally recommended for patients with gout, regardless of disease activity.

Limiting high-fructose corn syrup intake is conditionally recommended for patients with gout, regardless of disease activity.

Using a weight loss program (no specific program endorsed) is conditionally recommended for those patients with gout who are overweight/obese, regardless of disease activity.

Table 6. Gout flare management*

Recommendation	PICO question	Certainty of evidence
For patients experiencing a gout flare, we strongly recommend using oral colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or ACTH (the choice of colchicine, NSAIDs, or glucocorticoids should be made based on patient factors and preferences). When colchicine is the chosen agent, we strongly recommend low-dose colchicine over high-dose colchicine given its similar efficacy and fewer adverse effects.	32	High†
For patients experiencing a gout flare for whom other antiinflammatory therapies are poorly tolerated or contraindicated, we conditionally recommend using IL-1 inhibition over no therapy (beyond supportive/analgesic treatment).	33	Moderate
For patients who may receive NPO, we strongly recommend glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH.	32	High†
For patients experiencing a gout flare, we conditionally recommend using topical ice as an adjuvant treatment over no adjuvant treatment.	31	Low

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; IL-1 = interleukin-1; ACTH = adrenocorticotropic hormone; NPO = nothing by mouth (nulla per os).
† High quality of evidence from network meta-analyses supporting canakinumab, which has superior mean pain score reduction and mean day-2 joint tenderness reduction. However, the Voting Panel raised concern that the comparator was weak (triamcinolone 40 mg) and that cost issues significantly favor other agents.

Adding vitamin C supplementation is conditionally recommended *against* for patients with gout, regardless of disease activity.

The Voting Panel discussed data demonstrating the important genetic contributions to the development and severity of hyperuricemia and gout (92,93) and informally recommended that providers be mindful when soliciting information regarding the dietary habits of patients and ensure that discussions regarding dietary recommendations are not misinterpreted as "patient-blaming," as patients frequently feel stigmatized when discussing gout with their providers (94). Dietary modifications likely yield only small changes in SU concentration, but dietary factors may serve as triggers for flares, and patients frequently seek advice on dietary management (for recommendations for management of lifestyle factors, see Table 7 and Supplementary Figure 5, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract).

Alcohol. SU levels among patients who limited or abstained from alcohol were 1.6 mg/dl lower compared with patients who did not do so (95,96). Results from a recent diet and genetics meta-analysis that was noted above (92) demonstrated that the impact of diet or individual food items on SU concentration was small. As an example, a unit of beer raised SU concentrations by 0.16 mg/dl. The effects of a healthy diet, Mediterranean diet, or Dietary Approaches to Stop Hypertension (DASH) diet were even smaller (92).

In a case-crossover study, consuming >1–2 alcoholic beverage servings in the prior 24 hours was associated with a 40% higher risk of gout flare than periods without alcohol consumption, with a dose-response relationship (97). A small cohort study demonstrated that despite receiving ULT, heavy drinkers (≥30 units of alcohol/week) were more likely to continue having gout flares compared with those who do did not drink heavily (95).

Low purine diet. From the same case-crossover study noted above, there was a dose-response relationship between increasing purine intake and risk of gout flare (98). However, a small RCT (n = 29, with all participants receiving ULT with SU at target at the start of trial) using an educational intervention focused on low purine intake did not demonstrate lower SU concentrations compared with usual diet, despite significant improvements in patient dietary knowledge (99).

High-fructose corn syrup. The ingestion of 1 gm of fructose/kg of body weight increases SU concentration by 1–2 mg/dl within 2 hours of ingestion (100). In the National Health and Nutrition Examination Survey, artificially sweetened carbonated beverage consumption was associated with higher SU levels (101). In the Nurses' Health Study, greater consumption of high-fructose corn syrup was associated with higher risk of incident gout (102). However, there were no data focused on patients with existing gout.

Weight loss. The Voting Panel considered the impact of weight loss and specific dietary programs (including the DASH diet [103]). Due to small sample sizes, studies of patients without gout (or not defined), and risk of bias assessments, the certainty of the evidence was rated as very low for both SU and flares. Several studies and a systematic literature review (104) addressed weight loss approaches either directly (96,105) or indirectly (e.g., bariatric surgery [106,107], or dietary advice [108]). In a small cohort (n = 11) of obese patients, a mean weight loss of 5 kg resulted in a mean SU lowering of 1.1 mg/dl (96). In a large cohort study, obesity was associated with a higher risk of incident gout, but not recurrent gout flares (105). However, changes in body mass index (BMI) over time were associated with the risk of recurrent gout flare. An increase in BMI of >5% was associated with 60% higher odds of recurrent flare, and a decrease in BMI of >5% was associated with 40% lower odds of recurrent flare compared with those without weight change (–3.5% ≤ BMI ≤ 3.5%) (105). A small study of 12 patients undergoing bariatric surgery (mean 34.3 kg weight loss over 12 months) demonstrated a mean SU reduction of 2.0 mg/dl (106). Likewise, gout patients losing weight through bariatric surgery or diet experienced reduced flare frequency (108), although patients undergoing bariatric surgery may actually have

Table 7. Management of lifestyle factors*

Recommendation	PICO question	Certainty of evidence
For patients with gout, regardless of disease activity, we conditionally recommend limiting alcohol intake.	41	Low
For patients with gout, regardless of disease activity, we conditionally recommend limiting purine intake.	42	Low
For patients with gout, regardless of disease activity, we conditionally recommend limiting high-fructose corn syrup.	43	Very low
For overweight/obese patients with gout, regardless of disease activity, we conditionally recommend weight loss.	46	Very low
For patients with gout, regardless of disease activity, we conditionally recommend *against* adding vitamin C supplementation.	48	Low

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes.

a transient increase in flares risk during the first postoperative month (106).

Other dietary recommendations. The Voting Panel reviewed the data for cherries/cherry extract and dairy protein. The certainty of evidence drawn mainly from observational studies was low or very low, precluding specific recommendations on these topics. The Voting Panel reached consensus that data on vitamin C were insufficient to support continued recommendation for its use in patients with gout. Two small RCTs (n = 29 and n = 40) showed clinically insignificant changes in SU concentrations for patients with gout taking vitamin C (99,109).

Management of concurrent medications

Switching hydrochlorothiazide to an alternate antihypertensive when feasible is conditionally recommended for patients with gout, regardless of disease activity.

Choosing losartan preferentially as an antihypertensive agent when feasible is conditionally recommended for patients with gout, regardless of disease activity.

Stopping low-dose aspirin (for patients taking this medication for appropriate indications) is conditionally recommended *against* for patients with gout, regardless of disease activity.

Adding or switching cholesterol-lowering agents to fenofibrate is conditionally recommended *against* for patients with gout, regardless of disease activity.

Medications noted above are known to have effects on SU concentrations (110). The Voting Panel made recommendations specific to hydrochlorothiazide and losartan (111) in clinical scenarios where such changes are feasible. Switching, stopping, or adding a medication should only be considered when the potential SU concentration/gout benefits exceed the potential risks or harms of the medication change.

Recognizing that there are few practical alternatives to low-dose aspirin, the Voting Panel specifically recommended against its cessation as a means of SU reduction when a patient is taking it for an appropriate indication. Likewise, the Voting Panel specifically recommended against adding or switching cholesterol-lowering agents (e.g., statins, bile acid sequestrants, nicotinic acid agents, etc.) to fenofibrate despite its urate-lowering effects (112), as the risks, including side effects of the medication, were felt to outweigh potential benefits. Although likely to render only modest urate-lowering effects, switching from an angiotensin-converting enzyme inhibitor to losartan carries a risk that seems to be sufficiently low in most patients to merit this change when feasible (for all recommendations for management of concurrent medications, see Table 8 and Supplementary Figure 5, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24180/abstract).

DISCUSSION

This guideline reinforces many of the prior 2012 ACR Guidelines for the Management of Gout recommendations with updated literature and GRADE methodology, including incorporation of patient preferences and consideration of costs. The Voting Panel endorsed 42 recommendations overall, including 16 strong recommendations focused on ULT management (indications [n = 3], initiation [n = 6], titration and treat-to-target approach [n = 2], approaches following ULT failure [n = 2]), and flare management (n = 3).

Data from more recent RCTs comparing treat-to-target protocols versus usual care (43,61) provide the basis for the strong recommendation to use a treat-to-target strategy with ULT that includes a plan to achieve and maintain an SU target of <6 mg/dl to optimize patient outcomes. Findings from the evidence report resonated with the Patient Panel who concurred that their own SU levels correlated with related symptoms and changes in tophi. Patients on this panel articulated that SU assessments reinforced the importance of treatment adherence.

These guidelines reinforce the strategy of starting with low-dose ULT and titrating up to achieve the SU target. This strategy mitigates the risk of treatment-related adverse effects (e.g., hypersensitivity) as well as flare risk accompanying ULT initiation (39,41). Lacking data on optimal titration regimens, the Voting Panel indicated that titration should be individualized, based on available provider resources (e.g., staff for augmented delivery of care), patient preferences, the timing of ambulatory encounters,

Table 8. Management of concurrent medications*

Recommendation	PICO question	Certainty of evidence
For patients with gout, regardless of disease activity, we conditionally recommend switching hydrochlorothiazide to an alternate antihypertensive when feasible.	47	Very low
We conditionally recommend choosing losartan preferentially as an antihypertensive when feasible.	47	Very low
We conditionally recommend *against* stopping low-dose aspirin (in those who are taking this medication for appropriate indications).	47	Very low
We conditionally recommend *against* adding or switching to fenofibrate.	47	Very low

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes.

and antiinflammatory treatments. As described above, ULT titration should occur over weeks to months, not years. The 2012 ACR Guidelines for the Management of Gout recommended titration every 2–5 weeks (5). As noted in the ACR Clinical Quality Measures for Gout, SU concentrations should be checked after each dose titration (113). To limit the risk of ULT-related flares, these guidelines reinforce prior recommendations to use concurrent antiinflammatory prophylaxis for 3–6 months' duration, a shorter duration than advocated for in prior recommendations, but one that should be extended in the setting of frequent ongoing flares.

Breaking from prior ACR and European League Against Rheumatism (EULAR) guidelines, this guideline does not specify SU thresholds beyond <6 mg/dl for patient subsets with more severe disease (e.g., those with tophi). This guideline is not intended to contradict or dispute prior recommendations. There is ample evidence that lower SU levels hasten the resolution of tophi (23,114) and are associated with less frequent gout flares (26,114), suggesting that lower SU thresholds may be preferable for patients with more burdensome gout. However, in contrast to a treatment strategy using an SU target of <6 mg/dl as studied in clinical trials (43), there are no trial data to support lower specific thresholds for such patients.

In contrast to the 2012 ACR Guidelines for the Management of Gout (which did not consider treatment costs), this document firmly places allopurinol as the preferred first-line ULT for all patients, including those with CKD, due to the respective cost of each medication and potential CVD safety concerns that have recently emerged with febuxostat (72).

Under GRADE methodology, recommendations in these guidelines are supported by higher quality studies than the 2012 ACR Guidelines for the Management of Gout. This resulted in a more focused, less proscriptive document. Where certainty of data is less than moderate or high, conditional recommendations made herein are meant to highlight those decisions that would benefit from a shared patient-provider decision-making process. This would include areas such as diet, lifestyle, or concomitant medications that might affect SU levels, and for which the Patient Panel requested guidance. The Voting Panel aimed to provide guidance without implying any "patient-blaming" for the manifestations of gout given its strong genetic determinants.

Indications for ULT are expanded from the 2012 ACR Guidelines for the Management of Gout, but consistent with the 2016 update of the EULAR gout recommendations (10), to include individuals with evidence of radiographic damage attributable to gout (using any modality, regardless of subcutaneous tophi or flare frequency). This strong recommendation recognizes the various ways in which gout may present, and that joint damage is reflective of an active biologic process. Also added were conditional recommendations (which would warrant provider-patient shared medical decision-making discussion) for ULT use in patients with either infrequent flares (<2 flares/year) or a first flare with marked hyperuricemia (SU >9 mg/dl). Similar to the 2012 ACR Guidelines for the Management of Gout, the Voting Panel advocated a "medication-in-pocket" strategy for gout flare management, which the Patient Panel reinforced as a preferred approach.

This updated guideline effort also identifies several areas that inform a research agenda for gout management. While data support an active treat-to-target strategy, a question remains as to what may be the optimal SU threshold for patients with more severe disease, in addition to questions about threshold values in specific populations of gout patients. Gout has differential impact on patients by sex, race, or by presence of other comorbidities. This guideline is limited in commenting on specific groups of gout patients, as more studies of specific patient cohorts are needed in order to make differential recommendations. Additional studies are needed to determine the safety of prolonged and profound treatment-related hypouricemia (e.g., SU ≤3 mg/dl), an important knowledge gap given that epidemiologic studies have suggested an inverse association of SU concentration with select neurodegenerative disorders (115). While there are associations between SU and other comorbid conditions such as hypertension, CVD, and CKD (116), the benefit (or risk) of ULT in the absence of gout has yet to be established (117).

Gout has been characterized as a "curable disease" (118). As data continue to emerge supporting best practices in management, implementation of these recommendations will ideally lead to improved quality of care for patients with gout.

ACKNOWLEDGMENTS

We thank Theodore R. Fields, MD, FACP, Angelo L. Gaffo, MD, and Kenneth G. Saag, MD, for serving on the Expert Panel. We thank Jasvinder A. Singh for leading the Patient Panel meeting, as well as the patients who participated in this meeting: Lynn Brown, Jr., Douglas P. Davis, Larry Davis, Dextral L. Ely, Adam Paul Germek, Willie Earl Henton, James Edward Sims, and James Trucks. We thank N. Lawrence Edwards, MD, for his review of the manuscript. We thank Amit Aakash Shah, MD, MPH, for his assistance with the literature review. We thank the ACR staff, including Regina Parker for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, and Robin Lane for assistance in manuscript preparation. We thank Janet Joyce for help in developing the literature search strategy and performing the initial literature search, and Janet Waters for performing the update searches.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Neogi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Pregnancy-Lactation

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Rheumatology, 2022, **00**, 1–41
https://doi.org/10.1093/rheumatology/keac551
Guidelines

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Guidelines

British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids

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Keywords: rheumatic disease, pregnancy, breastmilk, breastfeeding, prescribing, corticosteroids, hydroxychloroquine, DMARDs, biologics

Received: 14 September 2022. **Accepted:** 15 September 2022

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Scope and purpose

Background

The rationale behind this update of the 2016 British Society for Rheumatology (BSR) guidelines on prescribing antirheumatic drugs in pregnancy and breastfeeding [1, 2] was described in detail in the guideline scope [3]. In brief, despite the existence of additional evidence-based guidelines on prescribing/managing rheumatic disease in pregnancy [4–7], the information contained within them requires continual review to include emerging information on the safety of new and existing drugs in pregnancy.

Chronic disease adversely affects pregnancy. Data from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) reports regularly from a national programme of work conducting surveillance and investigating the causes of maternal deaths, stillbirths and infant deaths [8]. Data from 2017–19 found that 8.8 women per 100 000 died during pregnancy or up to six weeks after childbirth or the end of pregnancy, and most women who died had multiple health problems or other vulnerabilities [8]. In all decisions regarding medication choices and changes, it is important to consider the potential for deterioration in the mother's wellbeing through side effects or reduced disease control (and its adverse impact on the baby). As such, the potential benefit to the foetus from any drug changes in the mother must be balanced against the possible risks to the foetus from loss of disease control in the mother [9].

Need for guideline

There has been an appreciable increase in the number of published pregnancy exposures to biologic DMARDs (bDMARDs), and two of these drugs are now licensed for use in pregnancy. In addition, therapeutic advances in management of various inflammatory rheumatic diseases (IRDs) have led to an expansion of bDMARDs and biosimilars with different modes of action, as well as a new class of targeted synthetic DMARDs (tsDMARDs).

The continuing expansion of existing and novel DMARDs means that uncertainty remains around the use of many of these drugs in pregnancy. This uncertainty may still lead to withdrawal of treatment from pregnant women unnecessarily [10]. Discontinuation of treatment in preparation for or during early pregnancy can increase the risk of disease activity and flares during pregnancy, and are reported following discontinuation of biologics in patients with IRDs [11]. The compatibility of various immunosuppressive and disease-modifying medications relevant to rheumatic disease will be covered in this update. This updated information will provide advice for healthcare professionals and patients, to ensure more confident prescribing in these scenarios, and will highlight any medications that should be stopped and/or avoided in the reproductive age group unless highly effective contraception is used, in line with guidance issued by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Faculty of Sexual and Reproductive Healthcare [12, 13].

Objectives of guideline

To update the previous BSR guidelines on prescribing in pregnancy in rheumatic disease of the following drug categories: antimalarials; corticosteroids; conventional synthetic (cs)DMARDs and immunosuppressive therapies; bDMARDs; and tsDMARDs. The full list of medications is shown in Supplementary Data S1, available at *Rheumatology* online. This revised guideline was produced by systematically reviewing all evidence published since the previous guideline, to answer specific questions in relation to each drug, as follows: Should it be stopped pre-conception? Is it compatible with pregnancy? Is it compatible with breastmilk exposure? Where possible, recommendations are made regarding compatibility with paternal exposure.

Target audience

The primary audience consists of health professionals in the UK directly involved in managing patients with rheumatic disease who are (or are planning to become) pregnant and/or breastfeeding, men with rheumatic disease who are planning to conceive, and patients with rheumatic disease who have unintentionally conceived while taking these medications. This audience includes rheumatologists, rheumatology nurses/allied health professionals, rheumatology speciality trainees and pharmacists, as well as the patients themselves. The guideline will also be useful to obstetricians, obstetric physicians, midwives, renal physicians, dermatologists, gastroenterologists, respiratory physicians and general practitioners who prescribe these medications in pregnancy.

This guideline uses the terms 'woman', 'maternal' or 'mother' throughout. These should be taken to include people who do not identify as women but are pregnant or have given birth [14]. Where the term 'breastfeeding' is used in this guideline it also refers to infant breastmilk exposure via other methods (e.g. expressed breastmilk, administered via a bottle).

The areas the guideline does not cover

This guideline does not cover the management of infertility or the indications for these drugs in specific rheumatic diseases in pregnancy. Other drug categories (pain management; NSAIDs and low dose aspirin; anticoagulants; bisphosphonates; anti-hypertensives; and pulmonary vasodilators) are considered in the BSR guideline on prescribing drugs in pregnancy and breastfeeding: comorbidity medications used in rheumatology practice (https://doi.org/10.1093/rheumatology/keac552). All recommendations in this guideline were formulated by the working group on the basis of published evidence at the time of the systematic literature search, and do not necessarily refer to licensing information or Summary of Product Characteristics for individual medications.

Stakeholder involvement

This guideline was commissioned by the BSR Standards, Guidelines and Audit Working Group. A Guideline Working group (GWG) was created, consisting of a chair (I.G.), alongside representatives from relevant stakeholders shown in Supplementary Table S1, available at *Rheumatology* online. In accordance with BSR policy, all members of the GWG made declarations of interest, available on the BSR website.

Involvement and affiliations of stakeholder groups involved in guideline development

The GWG consisted of rheumatologists from a range of clinical backgrounds, various allied health professionals, other specialists in women's health, lay members and representatives from the United Kingdom Teratology Information

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Service (UKTIS). All members of the working group contributed to the process for agreeing key questions, guideline content, recommendations and strength of agreement.

Rigour of development

Statement of scope of literature search and strategy employed

The evidence used to develop these guidelines was compiled from a systematic literature search conducted according to guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [15]. Studies were identified by searching MEDLINE and Embase databases from 1 January 2014 to 31 December 2020 using combinations of the key MESH and free terms: pregnancy; lactation; breastfeeding; paternal exposure; and the name of each drug. The full electronic search strategies for the MEDLINE and Embase databases are shown in Supplementary Data S2, available at *Rheumatology* online. Searches were not limited by disease indication; in addition to IRDs, studies in non-rheumatic diseases, such as psoriasis, inflammatory bowel disease (IBD) and organ transplantation were considered, if relevant. Additional published studies were identified through the Cochrane, LactMed (a National Library of Medicine database on drugs and lactation) and UKTIS databases (weblinks shown in Supplementary Data S2, available at *Rheumatology* online), and checking of reference lists from recently published national and international guidelines and systematic literature reviews. Due to the paucity of data pertaining to the use of non-TNFi biologic drugs and tsDMARDs in pregnancy and breastmilk exposure, relevant pharmaceutical companies were contacted between July and November 2021, and asked for any further available data.

Two independent reviewers screened the titles and abstracts of articles from the searches then reviewed the full texts of relevant studies, selecting articles that met inclusion criteria of: randomized and non-randomized controlled trials; cohort studies; case-control studies; and case series with more than ten participants. For medications with data on fewer than 300 pregnancy exposures, case series with more than five participants were eligible for inclusion. Conference abstracts were eligible for inclusion if they contained sufficient relevant data and there was no corresponding published manuscript. Case reports, and case series with fewer than five participants, were excluded, as were animal studies. Data extraction was performed by two reviewers. Disagreements arising during screening and extraction were resolved by group discussion, with involvement of a third reviewer where necessary.

Statement of methods used to formulate the recommendations (levels of evidence)

The working group met regularly to formalize the search strategy, review evidence, resolve disagreements and, finally, to determine recommendations. This guideline was developed in line with BSR's Guidelines Protocol using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology to determine quality of evidence and strength of recommendation. Accompanying each recommendation in this guideline, in brackets, is the strength of recommendation, quality of evidence and strength of agreement (SOA).

Strength of recommendation

Using GRADE, recommendations were categorized as either strong (denoted by 1) or weak (denoted by 2), according to the balance between benefits and risks. A strong recommendation was made when the benefits clearly outweigh the risks (or vice versa). A weak recommendation denotes that the benefits are more closely balanced with the risk or more uncertain.

Quality of evidence

Using the GRADE approach, the quality of evidence was determined as either high (A), moderate (B) or low/very low (C), reflecting the confidence in the estimates of benefits or harm.

Strength of agreement

The wording of each recommendation was revised until all members were satisfied that they would score at least 80 on a scale of 1 (no agreement) to 100 (complete agreement). The 20/24 working group members with full voting rights then scored each recommendation on the same scale, and the average was calculated to generate a strength of agreement (SOA) score. Two patient representatives and data analysts expressed concern that they did not have sufficient medical knowledge of all drugs reviewed to score all recommendations; so while they fully agreed with each recommendation, they did not wish to score each one, and did not contribute to the final SOA score.

Statement of any limits of search and when the guideline will be updated

The search was conducted in January 2021. Limits were placed for English language and filters as described above. The guideline will be updated in five years.

The guideline

A flow diagram of study selection is shown in Fig. 1, displaying the initial number of articles screened ($n = 27\,908$), the number of articles selected for full-length review ($n = 706$), and the number included in the final analysis from this

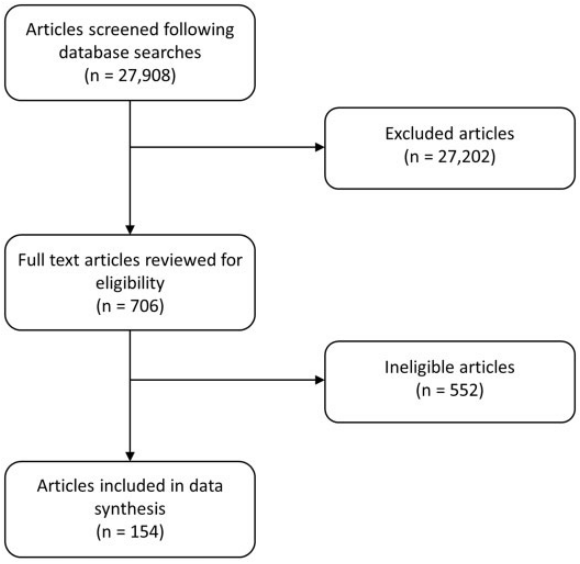
Articles screened following database searches (n = 27,908)
Excluded articles (n = 27,202)
Full text articles reviewed for eligibility (n = 706)
Ineligible articles (n = 552)
Articles included in data synthesis (n = 154)

Figure 1. Flow diagram of studies selected for inclusion

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updated search ($n = 154$). This information was then merged with the results of the previous guideline's systematic review to give the total exposure data for each drug. The following data were extracted where possible for each medication: number of studies and study type; number of pregnancy exposures; number of live births; pregnancy duration; birth weight; maternal complications; miscarriages; number and type of congenital anomalies (where possible, congenital anomalies described in original publications were classified as major/minor according to European surveillance of congenital anomalies (EUROCAT) definitions [16]); breastmilk exposure; long-term follow-up; and paternal exposure. An overall summary of compatibility of each drug pre-conception, during pregnancy, with breastmilk exposure, and with paternal exposure is shown in Table 1. For each drug, maternal information is summarized in the text and in Tables 2 and 3, while paternal exposures and recommendations are described separately and shown in Table 4. The data synthesis strategy for Tables 2–4 is shown in Supplementary Data S3, available at *Rheumatology* online. Other relevant papers identified in our search that did not meet the inclusion criteria are discussed in the main text.

Generic recommendations on prescribing immunomodulatory drugs and/or corticosteroids in rheumatic disease in pregnancy

i) Pre-conception counselling should be addressed by all healthcare professionals, with referral to professionals with relevant expertise as appropriate, to optimize disease control before pregnancy; with advice on the timing of pregnancy, and drug therapy before, during and after pregnancy, including contraception (GRADE 1A, SOA 99.5%).
ii) If a woman is planning pregnancy, avoid pregnancy-incompatible drugs (GRADE 1A, SOA 100%).
iii) The risks and benefits to the mother and foetus of drug treatment to control maternal disease should be discussed and clearly documented by all healthcare professionals involved in the patient's care (GRADE 1A, SOA 99.5%).
iv) Immunomodulatory drugs that are contraindicated in pregnancy should be switched to a pregnancy-compatible alternative in advance of conception to ensure maintenance of disease control on the new medication (GRADE 1A, SOA 100%).
v) When no pregnancy-compatible drugs are suitable, control of severe/life-threatening maternal disease should take priority over concerns for potential foetal outcomes (GRADE 1B, SOA 99.0%).
vi) All biologic DMARDs may be continued throughout pregnancy if required to control active/severe maternal disease (GRADE 1B, SOA 98.5%).
vii) Immunization schedules in infants after *in-utero* exposure to biologic DMARDs will depend on timing of exposure, bioavailability and persistence of the drug, mechanism of action of the drug, and live vaccines (GRADE 1C, SOA 99.5%).
viii) Where possible, the minimum effective dose of immunomodulatory drug or corticosteroid should be used to maintain maternal disease suppression, and stopping the drug during pregnancy may be considered in women at low risk of disease flare on withdrawal of therapy (GRADE 1B, SOA 100%).
ix) Some drugs may reduce male fertility, but paternal drug exposure in humans has not convincingly been associated with adverse foetal development or pregnancy outcome. Although the evidence is weak, men who take rheumatological medicines should be reassured about the safety of conceiving (GRADE 2C, SOA 98.4%).

Antimalarials

HCQ is the antimalarial drug most used to treat rheumatic disease and has been extensively studied in pregnancy. We identified an additional 23 studies [17–39] that, combined with the previous 23 studies [40–62], reported on ($n = 4701$) pregnancy exposures to HCQ, with very limited information on other antimalarials [17, 39, 63, 64]. Many of these studies were confounded by primarily reporting pregnancy outcomes in patients with SLE treated with other immunosuppressive agents, including MMF and corticosteroids, and use in anti-Ro/La positive patients in the prevention of congenital heart block (CHB). Despite these limitations, there were no appreciable adverse effects of HCQ on pregnancy duration or birth weight in the largest studies. In fact, several studies comparing HCQ-treated and untreated cohorts with rheumatic disease (mostly SLE) either found no significant difference between cohorts [17, 19, 21, 24, 28, 34, 36, 37], or significantly longer pregnancy durations and/or higher birth weight in the HCQ-treated pregnancies [18, 20, 22, 25, 27, 29, 30, 32, 33, 35]. The weighted mean for gestation across 15 studies reporting pregnancy duration in HCQ-exposed *vs* HCQ-unexposed pregnancies was 36.4 weeks and 34.7 weeks, respectively [18–21, 24, 27, 28, 30, 32–34, 36, 37, 43, 49]. The weighted mean for birth weight for HCQ-exposed *vs* HCQ-unexposed pregnancies was 2847 and 2733 g, respectively, in 10 studies reporting these outcomes [18, 20, 21, 27, 29, 33, 34, 36, 37, 43]. A total of 60 first trimester miscarriages were reported from 524 HCQ-exposed pregnancies (11.5%) in 10 studies, compared with 117 first trimester miscarriages in 718 HCQ-unexposed pregnancies (16.3%) [18–22, 27, 28, 30, 32, 33]. No specific pattern of congenital malformations was observed in association with HCQ exposure. No increased risk of adverse foetal outcomes was reported in >3229 chloroquine-exposed pregnancies in four studies [17, 39, 63, 64], including two studies where chloroquine was used as malaria prophylaxis during pregnancy; although, in these two studies, higher rates of maternal adverse events were reported, relative to the comparator (sulfadoxine-pyrimethamine). No information was found on mepacrine.

The findings for HCQ were consistent across all studies apart from a large population-based cohort study comparing HCQ-exposed ($n = 2045$) and HCQ-unexposed ($n = 21\,679$) pregnancies in patients with rheumatic disease, which did not control fully for disease, comorbidity-related pregnancy risk factors, dose of corticosteroids and combination with specific immunosuppressive drugs [23]. This study found a small increase in the risk of congenital malformations associated with first trimester HCQ use, mainly oral clefts, respiratory anomalies and urinary defects, with wide confidence intervals for specific malformations. A statistically significant increase in risk, however, was only found with daily doses of ≥400 mg of HCQ. This study concluded that for most patients with

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Table 1. Summary of drug compatibility in pregnancy and breastmilk exposure

	Peri-conception	First trimester	Second/third trimester	Breastfeeding	Paternal exposure
Corticosteroids					
Prednisolone	Yes	Yes	Yes	Yes	Yes
Antimalarials					
Hydroxychloroquine (≤400 mg/day)	Yes	Yes	Yes	Yes	Yes
Conventional synthetic DMARDs					
Methotrexate (≤25 mg/week)	Stop ≥1 month pre-conception	No	No	No	Yes
Sulfasalazine (with folic acid 5 mg/day in first trimester)	Yes	Yes	Yes	Yes[a]	Yes[b]
Leflunomide	No: Cholestyramine washout	No	No	No	Yes
Azathioprine	Yes	Yes	Yes	Yes	Yes
Ciclosporin	Yes	Yes[c]	Yes[c]	Yes	Yes
Tacrolimus	Yes	Yes[c]	Yes[c]	Yes	Yes
Cyclophosphamide	Exceptional circumstances[d]	Exceptional circumstances[d]	Exceptional circumstances[d]	No	No
Mycophenolate mofetil	Stop ≥6 weeks pre-conception	No	No	No	Yes
Intravenous immunoglobulin	Yes	Yes	Yes	Yes	Yes
Anti-TNFα medications					
Infliximab	Yes	Yes	Yes[e]	Yes	Yes
Etanercept	Yes	Yes	Yes[f]	Yes	Yes
Adalimumab	Yes	Yes	Yes[g]	Yes	Yes
Certolizumab	Yes	Yes	Yes	Yes	Yes
Golimumab	Yes	Yes	Yes[g]	Yes	Yes
Other biologic DMARDs					
Rituximab	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
IL-6 inhibitors	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
IL-1 inhibitors	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
Abatacept	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
Belimumab	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
IL-17 inhibitors	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
IL-12/23 inhibitors	Consider stopping at conception[h]	Severe disease if no alternatives[h]	Severe disease if no alternatives[i]	Yes[j]	Yes[j]
Targeted synthetic DMARDs					
JAK-inhibitors	Stop ≥2 weeks pre-conception	No	No	No	Yes[j]

For further information and caveats, see relevant recommendations and main text in the executive summary and full guideline.

[a] In the healthy, full-term infant only.
[b] If conception is delayed by >12months, consider stopping sulfasalazine alongside investigation of other causes of infertility.
[c] Suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels.
[d] Only in cases of severe (life or organ-threatening) maternal disease.
[e] If low risk of disease flare and stopped by 20 weeks, full-term infant can have a normal vaccination schedule.
[f] If low risk of disease flare and stopped by 32 weeks, full-term infant can have a normal vaccination schedule.
[g] If low risk of disease flare and stopped by 28 weeks, full-term infant can have a normal vaccination schedule.
[h] May be considered to manage severe maternal disease if no other pregnancy-compatible drugs are suitable.
[i] If used in third trimester, avoid live vaccinations in infant vaccination schedule until 6 months of age.
[j] Limited evidence.

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Table 2. Summary of maternal exposure to conventional synthetic DMARDs, antimalarials and corticosteroids

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
HCQ	31 ct [17–25, 27, 28, 30–39, 44–53] 1 rct [29] 1 nrt [26] 2 cc [42, 43] 3 cs [54–56] 6 cr [57–62] 2 sr [40, 41]	4701 (1st ≥3075, 2nd/3rd ≥583)	95/936	No significant adverse effect noted	162/3126 Overall, no increase in rate of major malformations attributable to drug	i) HCQ remains the antimalarial of choice in women planning a pregnancy with rheumatic disease in need of treatment, and should be continued during pregnancy at dose of ≤400 mg/day (GRADE 1B, SOA 100%) ii) HCQ is compatible with breastmilk exposure (GRADE 1B, SOA 99.5%)
Pred/MP	3 rct [84–86] 3 cc [43, 87, 88] 22 ct [31, 46, 48, 51–53, 71, 73–81, 89–95] 12 cs [55, 72, 96–105] 16 cr [55, 57, 59–61, 96–117] 1 Cochr [82] 1 sr [83]	2733 (1st ≥995, 2nd/3rd ≥637)	70/518	No significant adverse effect attributable to drug	63/697 No increase in rate of major malformations attributable to drug	i) Prednisolone is compatible with pregnancy and is the preferred corticosteroid in the treatment of maternal rheumatological disease in pregnancy and requires shared care with obstetric teams to monitor maternal blood pressure and blood glucose (GRADE 1B, SOA 100%) ii) Where possible, the dose of prednisolone should be <20 mg/day and tapered to the minimum effective dose to control maternal disease, in conjunction with steroid-sparing drugs compatible with pregnancy (GRADE 1C, SOA 99.5%) iii) Prednisolone is compatible with breastmilk exposure (GRADE 1B, SOA 100%) iv) Methylprednisolone has similar rates of placental transfer to prednisolone and would therefore be expected to be compatible with pregnancy and breastmilk exposure (GRADE 2C, SOA 99%)
MTX	2 cc [172, 181] 8 ct [37, 50, 52, 91, 179, 180, 182, 183] 1 cs [173] 5 cr [174–178]	766 (1st trimester ≥239, 2nd/3rd trimester ≥8)	80/479	Insufficient data; only one study reported birthweight in a cohort of $n = 23$ [37], with two studies reporting pregnancy duration ($n = 43$) [37, 181]	36/265 Individual case reports of MTX embryopathy, but larger studies show limited numbers of cases of foetal malformation	i) MTX at any dose should be avoided in pregnancy and stopped at least one month in advance of planned conception, when it should be switched to another pregnancy-compatible drug to ensure maintenance of maternal disease suppression (GRADE 1A, SOA 98%) ii) In women treated with low-dose (≤25 mg/week) MTX within one month prior to conception, folic acid supplementation (5 mg/day) should be continued up to 12 weeks of pregnancy (GRADE 1B, SOA 99.5%) iii) In unintended pregnancy on low-dose MTX (≤25 mg/week), there is minimal risk to the foetus; the drug should be stopped immediately, folic acid supplementation (5 mg/day) continued, and a careful evaluation of foetal risk with early referral to a foetal medicine department considered (GRADE 1C, SOA 100%) iv) Although only minute amounts of MTX are excreted into breastmilk, MTX cannot be recommended in breastfeeding because of theoretical risks and insufficient data on outcomes (GRADE 2C, SOA 99%)

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Table 2. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
SSZ	3 ct [46, 50, 52] 1 cs [55] 2 cr [62, 193]	178 (NR)	NR	No significant adverse effect noted	Rate not specifically quantified in the majority of papers. Overall, no increase in rate of major malformations attributable to drug	i) SSZ is compatible throughout pregnancy, with folic acid 5 mg/day recommended in the periconception period and during the first trimester (GRADE 1B, SOA 100%) ii) SSZ is compatible with breastmilk exposure in healthy, full-term infants (GRADE 1C, SOA 99.5%)
LEF	6 ct [50, 91, 194, 199–201] 4 cr [195–198]	814 (1st ≥156, 2nd/3rd ≥24)	138/811	No significant adverse effect noted	42/525 Overall, no increase in rate of major malformations attributable to drug, but most cases stopped in 1st trimester and received cholestyramine washout	i) LEF may not be a human teratogen but there remains insufficient evidence to support use at the time of conception or during pregnancy (GRADE 1B, SOA 98%) ii) Women on LEF considering pregnancy should stop and undergo a standard cholestyramine washout procedure, and switch to alternative medication compatible with pregnancy (GRADE 1B, SOA 98.8%) iii) If unintended conception occurs on LEF, the drug should be stopped immediately and a standard cholestyramine washout procedure given, with early referral to a foetal medicine department considered (GRADE 1B, SOA 99%) iv) LEF is not recommended while breastfeeding (GRADE 1C, SOA 99.5%)
AZA	5 cc [88, 135, 172, 203, 204] 16 ct [31, 45, 50–52, 78, 90, 92, 93, 95, 205, 206, 212–215] 6 cs [55, 99, 102, 173, 207, 208] 2 cr [61, 107] 1 sr [83]	1757 (1st ≥1254, 2nd/3rd ≥580)	130/642	No significant adverse effect noted	18/487 Overall, no increase in rate of major malformations attributable to drug	i) AZA is compatible throughout pregnancy (GRADE 1B, SOA 100%) ii) AZA is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)
CsA	4 cc [43, 88, 135, 136] 8 ct [50, 51, 92, 93, 95, 182, 219, 220] 3 cs [54, 101, 165]	401 (1st ≥131, 2nd/3rd ≥136)	9/132	Possible trend towards shorter pregnancy duration [92, 101, 136, 165] and low birth weight [88, 92, 165]	2/26 Data confounded by concomitant AZA/ MMF exposure	i) CsA is compatible throughout pregnancy with monitoring of maternal blood pressure, renal function, blood glucose and drug levels (GRADE 1B, SOA 100%) ii) CsA is compatible with breastmilk exposure (GRADE 2C, SOA 99.7%)
TAC	1 ct [92, 93, 219, 223, 225–231] 1 cs [99] 2 cr [107, 116]	515 (1st ≥302, 2nd/3rd ≥135)	108/451	Insufficient data to confirm lack of a significant adverse effect	12/270 Overall, insufficient data, mainly in organ transplant cohorts	i) TAC is compatible throughout pregnancy with monitoring of maternal blood pressure, renal function, blood glucose and drug levels (GRADE 2B, SOA 100%) ii) TAC is compatible with breastmilk exposure (GRADE 2C, SOA 99.8%)

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Table 2. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
CYC	1 cs [102] 4 cr [106, 111, 167, 168] 1 ct [232]	20 (1st ≥6, 2nd/3rd ≥2)	2/16	Insufficient data	0/13 Few data, from individual case reports or case series, available	i) CYC is a known teratogen and gonadotoxic, and therefore should only be considered in pregnancy in cases of severe life/organ-threatening maternal disease when there is appreciable risk of maternal and foetal morbidity and mortality without this therapy (GRADE 1B, SOA 99.5%) ii) CYC is not recommended while breastfeeding (GRADE 2C, SOA 100%)
MMF	7 ct [92, 95, 215, 242–245] 3 cs [99, 208, 235] 12 cr [57, 60, 113, 114, 116, 236–241]	804 (1st ≥796, 2nd/3rd ≥320)	371/753	Evidence of reduced pregnancy duration and birth weight	47/316 Data mainly from organ transplant cohorts, including one cohort of $n = 221$ demonstrating both reduced gestation and birth weight	i) MMF remains contraindicated during pregnancy, and should be avoided in women planning pregnancy or switched to a pregnancy-compatible alternative at least 6 weeks before attempting to conceive (GRADE 1B, SOA 100%) ii) In cases of unintended conception, switch MMF to a pregnancy-compatible alternative and refer to local experts for further advice and risk assessment (GRADE 1B, SOA 100%) iii) MMF is not recommended while breastfeeding (GRADE 2C, SOA 99.7%)
IVIG	1 cc [248] 12 ct [48, 49, 74, 79, 127, 128, 133, 249–253] 1 Cochr [82] 1 cs [97] 3 cr [58, 110, 254]	403 (1st ≥13, 2nd/3rd ≥77)	10/178	No significant adverse effect noted	22/121 Overall, no increase in rate of major malformations attributable to drug, albeit limited data available	i) IVIG is compatible with pregnancy (GRADE 1B, SOA 99.5%) ii) IVIG is compatible with breastmilk exposure (GRADE 2C, SOA 100%)

All studies that provided quantitative and/or qualitative information on the safety of the relevant drug in pregnancy were included; however, numerical outcome data could only be collated from papers where the relevant outcome was clearly quantified. Details of how numerical data in this table were derived are shown in Supplementary Data S3, available at *Rheumatology* online.
cc: case control; Cochr: Cochrane review; cr: case report; cs: case series; CsA: ciclosporin; ct: cohort; MP: methylprednisolone; NR: not reported; nrt: non-randomized trial; Pred: prednisolone; rct: randomised controlled trial; SOA: strength of agreement; sr: systematic review; TAC: tacrolimus.

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Table 3. Summary of maternal exposure to biological DMARDs and targeted synthetic DMARDs

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
TNFi (combined data for all licenced drugs)	See individual drugs below, plus: 28 ct [277, 278, 295–298, 301–313, 315–323] 1 cs [279] 4 cc [172, 299, 300, 314]	7787 (1st ≥2929, 2nd/3rd ≥2150)	886/4192	No significant adverse effect noted overall	214/5157 Overall, no increase in rate of major malformations attributable to drug	i) Women with no/low disease activity established on a tumour necrosis factor inhibitor (TNFi) with known placental transfer (INF, ADA, GOL) do not need to be switched to an alternative TNFi with established minimal placental transfer (CZP) either before or during pregnancy (GRADE 1B, SOA 100%) ii) CZP is compatible with all three trimesters of pregnancy, has no to minimal placental transfer compared with other TNFi, and does not require any alteration to the infant vaccination schedule (GRADE 1B, SOA 100%) iii) Women considered to have low risk of disease flare on withdrawal of TNFi in pregnancy could stop INF at 20 weeks, ADA and GOL at 28 weeks, and ETA at 32 weeks so that a full-term infant can have a normal vaccination schedule, with rotavirus vaccination at 8 weeks as per the UK schedule (GRADE 1B, SOA 99.5%) iv) INF, ADA, ETA or GOL may be continued throughout pregnancy to maintain maternal disease control; in these circumstances, live vaccines should be avoided in infants until they are 6 months of age (GRADE 1B, SOA 100%) v) If a TNFi is stopped in pregnancy, it can be restarted as soon as practical post-partum in the absence of infections or surgical complications, regardless of breastfeeding status, to ensure control of maternal disease (GRADE 1C, SOA 100%) vi) TNFi are compatible with breastmilk exposure (GRADE 1C, SOA 100%)
CZP	2 ct [283, 284] 1 cs [285]	567 (1st ≥371, 2nd/3rd ≥335)	52/567	No significant adverse effect noted overall	9/488 Overall, no increase in rate of major malformations attributable to drug	See recommendations above
INF	9 ct [50, 260–263, 291–294] 8 cs [173, 264–270] 1 cr [271]	2645 (1st ≥1301, 2nd/3rd ≥92)	255/2484	No significant adverse effect noted overall	56/2090 Overall, no increase in rate of major malformations attributable to drug	See recommendations above
ETA	5 ct [50, 52, 260, 286, 287] 3 cs [100, 266, 272] 4 cr [108, 109, 273, 274] 1 rct [288]	821 (1st ≥475, 2nd/3rd ≥207)	73/383	No significant adverse effect noted overall	47/676 Overall, no increase in rate of major malformations attributable to drug	See recommendations above

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Table 3. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
ADA	7 ct [50, 52, 252, 261, 280–282] 5 cs [99, 266, 268–270] 3 cr [271, 275, 276]	473 (1st ≥425, 2nd/3rd ≥298)	33/371	No significant adverse effect noted overall	30/397 Overall, no increase in rate of major malformations attributable to drug	See recommendations above
GOL	2 ct [289, 290]	166 (NR)	34/166	NR	3/115 Overall, no increase in rate of major malformations attributable to drug	See recommendations above
RTX	5 ct [50, 343, 344, 350, 354] 4 cs [345, 351–353] 4 cr [346–349]	316 (1st ≥13, 2nd/3rd ≥1)	68/293	No significant adverse effect noted	6/170 Overall, no increase in rate of major malformations attributable to drug	i) Limited evidence has not shown RTX to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception (GRADE 2C, SOA 99.3%) ii) RTX may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.7%) iii) If RTX is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 98.7%) iv) Based on limited evidence, maternal treatment with RTX is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)
TOC	2 ct [358, 359] 2 cs [356, 357]	365 (1st ≥46, 2nd/3rd ≥2)	84/354	No significant adverse effect attributable to drug (data limited by confounding)	8/211 Overall, no increase in rate of major malformations attributable to drug	i) Limited evidence has not shown IL-6i to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.7%) ii) IL-6i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 100%) iii) If IL-6i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%) iv) Based on limited evidence, maternal treatment with IL-6i is compatible with breastmilk exposure (GRADE 2C, SOA 100%)

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Table 3. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
ANA	2 ct [50, 371] 4 cs [367, 369, 370, 372] 1 cr [368]	48 (1st ≥25, 2nd/3rd ≥40)	3/43	No significant adverse effect attributable to drug	2/41 (including one resulting in miscarriage at 30 weeks)	i) Limited evidence has not shown IL-1i to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.8%) ii) IL-1i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 100%) iii) If IL-1i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%) iv) Based on limited evidence, maternal treatment with IL-1i is compatible with breastmilk exposure (GRADE 2C, SOA 100%)
CAN	1 cs [369]	8 (all 1st)	1/8	No significant adverse effect noted	0/7	See recommendations above
ABA	1 cs [175] 1 cr [349] 2 ct [375, 376]	99 (1st ≥145, 2nd/3rd ≥10)	49/187	No significant adverse effect attributable to drug (data limited by confounding)	10/104 Overall, no pattern of malformations attributable to drug	i) Limited evidence has not shown ABA to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%) ii) ABA may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.3%) iii) If ABA is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%) iv) Based on limited evidence, maternal treatment with ABA is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)

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Table 3. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
BEL	1 ct [380]	66 (NR)	18/66	No significant adverse effect attributable to drug (data limited by confounding)	3/33 Overall, no pattern of malformations attributable to drug	i) Limited evidence has not shown BEL to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%) ii) BEL may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.5%) iii) If BEL is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 98.8%) iv) Based on limited evidence, maternal treatment with BEL is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)
SEC	2 ct [387, 388]	244 (1st ≥161, 2nd/3rd NR)	26/125	No significant adverse effect noted	2/54 Overall, no pattern of malformations attributable to drug	i) Limited evidence has not shown IL-17i to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%) ii) IL-17i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99%) iii) If IL-17i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%) iv) Based on limited evidence, maternal treatment with IL-17i is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)
IXE	1 ct [389]	18 (NR)	5/18 (spontaneous and induced)	No significant adverse effect noted	0/8 Overall, no pattern of malformations attributable to drug	See recommendations above

(continued)

Table 3. (continued)

Drug	Studies (type and number)	Pregnancy exposures (exposures per trimester)	Foetal losses/ total pregnancy outcomes	Pregnancy duration and birth weight	Malformations/total births	Recommendation (GRADE/Strength of agreement)
UST	2 ct [391, 392] 1 cs [393]	517 (1st ≥31, 2nd/3rd ≥10)	92/517	No significant adverse effect noted	17/375 Overall, no pattern of malformations attributable to drug	i) Limited evidence has not shown UST to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%) ii) UST may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 98.8%) iii) If UST is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%) iv) Based on limited evidence, maternal treatment with UST is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%)
TOF	1 ct [397]	116 (all 1st, 2nd/3rd NR)	15/72	No significant adverse effect noted	2/44 Overall, no pattern of malformations attributable to drug	i) There are insufficient data to make a recommendation on JAKi use during pregnancy and they should be stopped at least two weeks before planned conception (GRADE 2C, SOA 99.5%) ii) There are insufficient data to recommend JAKi in breastfeeding and, given they are likely to transfer into breastmilk, they should be avoided (GRADE 2C, SOA 99.5%)

All studies that provided quantitative and/or qualitative information on the safety of the relevant drug in pregnancy were included; however, numerical outcome data could only be collated from papers where the relevant outcome was clearly quantified. Details of how numerical data in this table were derived are shown in Supplementary Data S3, available at *Rheumatology* online.
ABA: abatacept; ADA: adalimumab; ANA: anakinra; BEL: belimumab; CAN: canakinumab; cc: case control; cr: case report; cs: case series; ct: cohort; CZP: certolizumab; ETA: etanercept; GOL: golimumab; IL-1i: IL-1 inhibitors; IL-6i: IL-6 inhibitors; IL-17i: IL-17 inhibitors; INF: infliximab; IXE: ixekizumab; JAKi: Janus kinase inhibitor; NR: not reported; rct: randomized controlled trial; RTX: rituximab; SEC: secukinumab; SOA: strength of agreement; TNFi: TNF-alpha inhibitor; TOC: tocilizumab; TOF: tofacitinib; UST: ustekinumab.

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Table 4. Summary of pregnancy outcomes after paternal exposure

Drug	Studies included (type and number)	Pregnancy exposures	Adverse pregnancy outcomes (foetal losses or malformations)	Recommendation (GRADE/Strength of agreement)
HCQ	1 ct [52] 1 cs [404]	13	No increase	Paternal exposure to HCQ is compatible with pregnancy (GRADE 2C, SOA 99.3%)
CS	5 ct [52, 405–407, 411] 2 cs [404, 408]	4507	No increase	Paternal exposure to prednisolone is compatible with pregnancy (GRADE 1B, SOA 99.3%)
SSZ	3 ct [52, 407, 412] 1 cc [409]	237	No increase	Men who take SSZ may have reduced fertility. There is little evidence to suggest that SSZ should be stopped pre-conception, unless conception is delayed by >12 months when stopping SSZ should be considered along with other causes of infertility (GRADE 1C, SOA 99.0%)
LEF	1 ct [52] 1 cr [413]	2	No increase	Paternal exposure to LEF is compatible with pregnancy (GRADE 2C, SOA 99.3%)
AZA	9 ct [52, 185, 187, 216, 405–407, 414, 415] 1 cc [409] 2 cs [404, 408]	3282[a]	No increase	Paternal exposure to AZA is compatible with pregnancy (GRADE 1B, SOA 99.3%)
MTX	10 ct [52, 184–189, 405, 407] 3 cs [404, 410], 1 cr [428]	2289	No increase	Paternal exposure to low-dose (≤25 mg/week) MTX is compatible with pregnancy (GRADE 1B, SOA 99.3%)
CsA	3 ct [185, 406, 416] 2 cs [408, 410]	501[a]	No increase	Paternal exposure to CsA is compatible with pregnancy (GRADE 1C, SOA 99.3%)
TAC	3 ct [406, 416, 417]	41[a]	No increase	Paternal exposure to TAC is compatible with pregnancy (GRADE 2C, SOA 99.3%)
CYC	No data meeting inclusion criteria		Known to affect male fertility; evidence of an adverse impact on germ cell development and male-mediated teratogenicity from animal studies	Due to the adverse effect of CYC on male fertility, semen cryopreservation is recommended for men prior to paternal exposure (GRADE 1C, SOA 99.5%)
MMF	3 ct [185, 246, 247] 3 cs [406, 416, 426]	292	No increase	Paternal exposure to MMF is compatible with pregnancy (GRADE 2C, SOA 99.3%)
TNFi	13 ct [52, 263, 293, 298, 306, 405, 412, 427, 430–434] 2 cs [404, 410] 2 cr [428, 429] 1 cc [409]	751	No increase	Paternal exposure to TNFi is compatible with pregnancy (GRADE 1C, SOA 99.3%)
RTX	1 ct [343]	11	No increase	Paternal exposure to RTX is compatible with pregnancy (GRADE 2C, SOA 99.3%)
IL-6i	1 ct [359]	15 (TOC)	No increase	Paternal exposure to IL-6i is compatible with pregnancy (GRADE 2C, SOA 99.3%)
IL-1i	1 ct [369]	5 (ANA) 6 (CAN)	No increase	Paternal exposure to IL-1i is compatible with pregnancy (GRADE 2C, SOA 99.3%)
ABA	1 ct [375]	10	No increase	Paternal exposure to ABA is compatible with pregnancy (GRADE 2C, SOA 99.3%)
IL-17i	2 ct [387, 389]	54 (SEC) 34 (IXE)	No increase	Paternal exposure to IL-17i is compatible with pregnancy (GRADE 2C, SOA 99.3%)
JAKi	1 ct [398]	87 (TOF)	No increase	Paternal exposure to JAKi is compatible with pregnancy (GRADE 2C, SOA 99.3%)

All studies that provided quantitative and/or qualitative information on the safety of the relevant drug following paternal exposure were included. Details of how numerical data in this table were derived are shown in Supplementary Data S3, available at *Rheumatology* online.

[a] Minimum number of pregnancy exposures to drug; additional exposures were described in some studies but could not be separated from grouped study data.

ABA: abatacept; ANA: anakinra; BEL: belimumab; CAN: canakinumab; cc: case control; cr: case report; cs: case series; CS: corticosteroids; CsA: ciclosporin; ct: cohort; IL-1i: IL-1 inhibitors; IL-6i: IL-6 inhibitors; IL-17i: IL-17 inhibitors; IXE: ixekizumab; JAKi: Janus kinase inhibitors; NR: not reported; RTX: rituximab; SEC: secukinumab; SOA: strength of agreement; TAC: tacrolimus; TNFi: TNF-alpha inhibitor; TOC: tocilizumab; TOF: tofacitinib; UST: ustekinumab.

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autoimmune rheumatic disorders, the benefits of treatment during pregnancy will likely outweigh this risk.

Importantly, a more recent study (published after our search date) of pregnant women prospectively enrolled into MotherToBaby/Organisation of Teratology Information Specialists (OTIS) pregnancy studies, compared outcomes for HCQ-exposed pregnancies ($n = 279$) with disease-matched ($n = 279$) and healthy comparator ($n = 279$) HCQ-unexposed groups [65]. Reassuringly, this study found no evidence of an increased risk for structural defects or other adverse outcomes with HCQ at any dose (average 325 mg/day; range 100–800 mg/day), except for an isolated finding of reduced head circumference at birth with HCQ exposure, which was not thought to be of any clinical significance.

Therefore, advice on HCQ dosage in pregnancy relates to general guidance for reducing ophthalmic risk outside of pregnancy to a maximum of 400 mg/day, as pharmacokinetic changes in pregnancy reduce the reliability of weight-based dosing [66]. Ultimately, it is important to maintain HCQ during pregnancy, as discontinuation of this drug in pregnancy may increase risk of disease flares and foetal loss [67]. Disease flares would increase the need for alternative medications with more potential risks for mother or baby in pregnancy.

Previous studies of breastmilk exposure to HCQ were mostly limited to case reports, showing that <1% of the maternal dose of HCQ was found in breastmilk [68]. Three more recent studies of HCQ use ($n = 195$) confirmed very low concentrations of HCQ in breastmilk and no adverse effects on breastfed infants [36, 69, 70]. There remain limited studies of long-term outcomes in children, but no adverse immunological or clinical findings have been reported [36, 43].

Recommendations for hydroxychloroquine in pregnancy and breastmilk exposure

i) HCQ remains the antimalarial of choice in women planning a pregnancy with rheumatic disease in need of treatment, and should be continued during pregnancy at a dose of ≤400 mg/day (GRADE 1B, SOA 100%).
ii) HCQ is compatible with breastmilk exposure (GRADE 1B, SOA 99.5%).

Corticosteroids

Corticosteroids used to treat rheumatic disease (prednisolone, prednisone and methylprednisolone) are metabolized in the placenta, and so 10% or less of the active drug reaches the foetus. Previously, we identified 47 studies on prednisolone and found it to be compatible with pregnancy and breastmilk exposure [1]. Studies of corticosteroid use in pregnancy were confounded by multiple concomitant medications and use in high-risk pregnancies; particularly the fluorinated steroids, which are used to prevent or treat preterm labour and complications such as foetal lung immaturity. Therefore, we searched for further evidence on corticosteroids used to treat rheumatic disease and identified additional studies: 11 on prednisolone with ($n = 1218$) pregnancies [31, 71–80] and one on methylprednisolone with ($n = 12$) pregnancies [81]. This evidence was combined with the previous studies: 47 on prednisolone ($n = 1503$) [43, 46, 48, 51–53, 55, 57, 59–61, 82–117]; 31 on dexamethasone ($n = 11\,214$) [48, 54, 88, 97, 118–144]; 27 on betamethasone ($n = 27\,746$) [118–120, 125, 126, 128, 130, 131, 140, 143, 145–162]; and 10 on general corticosteroid use ($n = 785$) [42, 49, 50, 54, 163–168].

Studies on the use of methylprednisolone in pregnancy were not specifically sought in the previous guideline because it is generally used as rescue therapy for severe disease. Compared with prednisolone, parenteral administration of methylprednisolone has a prolonged duration of action with similar rates of placental transfer to prednisolone [169].

Previously, we found that following prednisolone (or unspecified corticosteroid) exposure, average pregnancy duration in the majority of randomized controlled trial (RCT), case-control, cohort and case-series studies (where reported) was usually term, at ≥37 weeks [43, 51, 84, 85, 88, 92, 94, 96, 101, 102, 104, 105]. Other studies reporting ≤37-week delivery were confounded by factors such as maternal disease and concomitant medications [46, 57, 59, 60, 86, 87, 99, 106, 113, 117, 163, 165]. Birth weights followed a similar pattern and were affected by preterm deliveries and confounding factors, as described above. For instance, prednisolone exposure in those RCTs, cohorts, case-control studies and case series which reported average gestations of ≥37 weeks, average birth weights ranged from 2.6–3.4 kg [43, 46, 51, 85, 88, 92, 94, 96, 101, 104, 105]. Overall, prednisolone itself was not felt to have contributed to low birth weight (LBW) in any study [1].

High rates of maternal complications compatible with underlying disease were previously reported for prednisolone and dexamethasone, but none were specifically attributed to these medications [1]. The major congenital malformations observed with prednisolone were frequently confounded by concomitant teratogenic drug exposure, such as MMF [116], and the overall incidence was not significantly higher than in drug-free controls. Studies reporting major malformations with fluorinated steroid exposure [e.g. patent ductus arteriosus (PDA), blindness and deafness [126, 145]] did not attribute them to steroid therapy. Furthermore, in the majority of cases, the steroids were used for treatment of underlying conditions such as preterm delivery [126], where steroids were found to be beneficial in improving outcomes, or treatment of maternal autoantibody-mediated cardiomyopathy [133]. A large study analysing 832 636 live births did not show an increased risk of orofacial cleft palate with the use of corticosteroids in pregnancy [164]. foetal loss in studies of prednisolone and fluorinated steroids was attributed to underlying disease rather than steroid therapy, such as in APS [105] and complete atrio-ventricular block [170].

Most (8/11) of the additional studies on maternal prednisolone exposure that we found in our updated search did not identify any adverse effects of prednisolone use on pregnancy outcomes [31, 72–74, 76–79]. In contrast, a population-based study from Norway exploring the associations between disease activity and medications with offspring birth weight, pre-eclampsia and preterm birth in SLE found prednisolone use to be significantly associated with lower birth weight, increased risk of pre-eclampsia, and a 3-fold increase in preterm birth [71]. A conference abstract reported that continuation of high-dose glucocorticoids during 164 pregnancies increased the risks of preterm birth, low birth weight and preterm premature rupture of membranes (PPROM) at prednisolone cut-off doses of 7.5 mg, 6.7 mg, 5.0 mg per day, respectively [75]. In contrast, another conference abstract of 143 SLE pregnancies found that foetal complications were associated with prednisone >25 mg, and that low (10 mg/day) to moderate (10–24 mg/day) doses of prednisone during pregnancy were not associated with adverse foetal outcomes [77]. Similarly, the largest prospective study of SLE pregnancy outcomes did

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not identify prednisolone ≤20 mg/day as a risk factor for adverse pregnancy outcomes [31].

UKTIS notes that many of the studies reporting pregnancy outcomes following gestational exposure to systemic corticosteroids are limited by a lack of stratification to account for differing doses, treatment duration and steroid potencies, as well as confounding by maternal disease [171]. It concludes that preterm delivery may be associated with gestational exposure to systemic corticosteroids, and further well-controlled studies are required to address this question. Therefore, an increased risk of adverse foetal effects following use of high-dose/potency corticosteroids, or use for extended periods, cannot be ruled out.

Based on limited evidence, prednisone, prednisolone and methylprednisolone are considered compatible with breastmilk exposure [1]. There remain few breastmilk exposure studies. One study, comprising 19 pregnancy and breastmilk exposures, found that prednisone and prednisolone exhibit dose- and concentration-dependent pharmacokinetics during pregnancy, and infant exposure to these agents via breastmilk is minimal [76]. Another study of 12 patients with multiple sclerosis found the transfer of methylprednisolone into breastmilk to be low even when maternal serum concentration levels were highest at the end of an infusion, and although these levels were not considered to pose a threat to the infant, they state that mothers may choose to wait two to four h to further limit an infant's exposure [81].

Previously, long-term follow-up studies had not reported any adverse events after prednisolone exposure in pregnancy [1]. Two additional studies did not report any adverse events from 9–12 months of post-partum follow-up of 227 non-rheumatic disease pregnancies exposed to prednisolone [78, 79].

Recommendations for corticosteroids in pregnancy and breastmilk exposure

i) Prednisolone is compatible with pregnancy and is the preferred corticosteroid in the treatment of maternal rheumatological disease in pregnancy and requires shared care with obstetric teams to monitor maternal blood pressure and blood glucose (GRADE 1B, SOA 100%).
ii) Where possible, the dose of prednisolone should be <20 mg/day and tapered to the minimum effective dose to control maternal disease, in conjunction with steroid-sparing drugs compatible with pregnancy (GRADE 1C, SOA 99.5%).
iii) Prednisolone is compatible with breastmilk exposure (GRADE 1B, SOA 100%).
iv) Methylprednisolone has similar rates of placental transfer to prednisolone and would therefore be expected to be compatible with pregnancy and breastmilk exposure (GRADE 2C, SOA 99%).

Conventional synthetic DMARDs and immunosuppressive therapies

Methotrexate

MTX is contraindicated in pregnancy and was previously recommended to be stopped at least three months in advance of conception [68]. UKTIS considers MTX risk in pregnancy to be dependent on its use at high (>25 mg per week) or low (≤25 mg per week) dosages [171]. Rheumatology usage of MTX to treat inflammatory arthritis falls into the low-dose category and is far removed from the high doses used as a chemotherapeutic agent in the treatment of various cancers (e.g. >500 mg/m^2) or as an abortifacient at 50 mg/m^2. UKTIS concludes that exposure to high-dose MTX in early pregnancy confers a risk of severe embryopathy (including craniofacial defects, malformations of the digits and defects of the spine and ribs) in the foetus, and the option of termination of pregnancy should be discussed with the patient. In contrast, for exposure to lower doses of MTX prior to conception, additional foetal monitoring is advised, as well as counselling of women and their partners about the lack of available data to facilitate quantification of risk of adverse pregnancy outcomes.

Previously, we identified a high proportion of major anomalies following MTX (and other DMARD) exposure, predominantly during the first trimester of pregnancy, in 27 pregnancies from 10 studies [50, 52, 91, 172–178]. An additional 12 studies of MTX exposure in 2765 pregnancies were identified: six maternal studies [37, 179–183] and six paternal studies [184–189].

Several studies reported on the risks of pre-conceptual and pregnancy exposure to MTX. Data from the National Birth Defects Prevention Study, a US case-control study of major birth defects, reported that 4/10 113 (0.04%) mothers of foetus/infants without major birth defects (controls) had been exposed to MTX, compared with 16/27 623 (0.06%) mothers of live-born infants with a major birth defect (cases) who had been exposed to MTX [181]. The dose of MTX was not reported, but indications included a neoplasm of endocrine glands and so was presumably of high dose in at least one case. Of the 16 cases with major birth defects, 15 were exposed from three months pre-conception to the end of the first trimester.

A cohort study of 240 SLE pregnancies in whom 36.8% were exposed to MTX before and during the first trimester reported an increased risk of foetal complications [182]. A large prospective observational multicentre cohort study of 324 pregnancies exposed to MTX found an increase in the cumulative incidence of spontaneous miscarriage (42.5%) and major congenital anomalies (6.6%) among pregnancies ($n = 188$) exposed to a median dose of 10 mg/week of MTX after a median of 4.3 weeks post-conception [179]. This difference reached statistical significance when compared with a cohort of women without autoimmune diseases, but not when compared with a disease-matched cohort. No increased risk of miscarriage or major congenital anomaly was found in pregnancies ($n = 136$) exposed to a median dose of 15 mg/week of MTX that was stopped three months pre-conception.

Not all studies reported increased risks with MTX exposure. A study of pre-conception use of MTX on miscarriage rates in 114 RA pregnancies, compared with 48 MTX-unexposed RA pregnancies, did not find a statistically significant association between miscarriage and MTX use [180]. An analysis of 18 pregnancies exposed to MTX (≤20 mg/week) from up to one year pre-conception and in the first trimester found a high percentage of live-born children with no malformations [183]. Analysis of 23 first trimester exposures to low-dose MTX, identified from three United States health plan databases, did not reveal a significant increase in the risk of congenital malformations, foetal death or neonatal complications in women with chronic autoimmune disease, compared with those who received MTX before, but not during, pregnancy [37].

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These studies provide some evidence that a 3-month MTX-free interval prior to conception might not be required. Therefore, unintentional exposure to low-dose MTX during the peri-conceptional period confers minimal risk in unintended pregnancy exposures, and so termination of pregnancy is not routinely recommended for MTX exposure unless it is maternally requested due to unplanned pregnancy [37, 180, 183].

Studies of MTX in breastfeeding remain very limited. Although they did not meet our inclusion criteria, we identified two case reports that found low levels of MTX in breastmilk and no adverse effects on the breastfed infants [190, 191]. LactMed describes low levels of MTX in breastmilk and conflicting expert opinion on whether it can safely be used during breastfeeding [192]. It states that withholding breastfeeding for 24 h after a weekly low-dose of MTX may decrease the infant's dose by 40%, and that if breastfeeding is undertaken during long-term, low-dose MTX use, monitoring of the infant's complete blood count and differential could be considered.

Post-partum follow-up of up to 14 months after first trimester MTX exposure was reported in three infants with long-term complications of foetal MTX syndrome, including semi lobar holoprosencephaly, cardiac abnormalities, tracheostomy and requirement for antiepileptic therapy [176, 177].

Recommendations for methotrexate in pregnancy and breastmilk exposure

i) MTX at any dose should be avoided in pregnancy and stopped at least one month in advance of planned conception, when it should be switched to another pregnancy-compatible drug to ensure maintenance of maternal disease suppression (GRADE 1A, SOA 98%).
ii) In women treated with low-dose (≤25 mg/week) MTX within one month prior to conception, folic acid supplementation (5 mg/day) should be continued up to 12 weeks of pregnancy (GRADE 1B, SOA 99.5%).
iii) In unintended pregnancy on low-dose (≤25 mg/week) MTX, there is minimal risk to the foetus; the drug should be stopped immediately, folic acid supplementation (5 mg/day) continued, and a careful evaluation of foetal risk with early referral to a foetal medicine department considered (GRADE 1C, SOA 100%).
iv) Although only minute amounts of MTX are excreted into breastmilk, MTX cannot be recommended in breastfeeding because of theoretical risks and insufficient data on outcomes (GRADE 2C, SOA 99%).

Sulfasalazine

Previously, we recommended that SSZ is compatible with pregnancy and breastmilk exposure and can be continued with adequate folic acid supplementation (5 mg/day) [1]. This recommendation was based on six publications reporting SSZ exposure in 178 pregnancies in patients with RA, osteoporosis and ankylosing spondylitis (AS) [46, 50, 52, 55, 62, 193]. These studies contained limited information relating to miscarriage rate, pregnancy duration, birth weight or malformation rate; overall, however, there were no significant adverse effects highlighted that were considered to be directly attributable to SSZ. We did not identify any additional studies on the use of SSZ in pregnancy, breastmilk exposure or paternal exposure.

UKTIS does not identify any specific risks with SSZ exposure. It comments that although high-dose folic acid (5 mg/day) is generally recommended, no studies have investigated whether there is increased benefit of this higher dose of folic acid compared with a standard dose of 400 micrograms/day.

Minimal amounts of SSZ are expressed in breastmilk, and it can be used during breastfeeding if the infant is full term and healthy, although it should be avoided in ill, stressed or premature infants, and in infants with hyperbilirubinaemia or glucose-6-phosphate dehydrogenase deficiency [68].

Recommendations for sulfasalazine in pregnancy and breastmilk exposure

i) SSZ is compatible throughout pregnancy, with folic acid 5 mg/day recommended in the periconception period and during the first trimester (GRADE 1B, SOA 100%).
ii) SSZ is compatible with breastmilk exposure in healthy, full-term infants (GRADE 1C, SOA 99.5%).

Leflunomide

Based upon limited evidence, we previously found that LEF may not be a human teratogen, but there was insufficient evidence to support its compatibility in human pregnancy, so our recommendation was that LEF is not the DMARD of choice in women planning pregnancy [1]. This recommendation was based on data from seven studies [50, 91, 194–198] reporting on 111 pregnancies exposed to LEF (discontinued in almost all cases in the first trimester, and frequently followed by a cholestyramine washout). Overall, the findings were largely reassuring, with no direct evidence of human teratogenicity.

We identified three additional studies of 703 pregnancies exposed to LEF at various stages of pregnancy, with varying exposure to washout and/or plasma testing of LEF metabolites, which did not find an increased risk of adverse pregnancy outcomes compared with the general population [199–201]. Although it was not included within our systematic review, pregnancy outcomes have been reported for teriflunomide—the principal active metabolite responsible for leflunomide's activity *in vivo*—which, at recommended doses, results in a similar range of plasma concentrations to leflunomide [202]. The known outcomes from 222 pregnancy exposures to teriflunomide for relapsing forms of multiple sclerosis also found outcomes consistent with the general population [202]. Overall, these findings do not indicate a teratogenic risk of LEF in human pregnancies. The practicality of previous recommendations regarding the testing of plasma levels of teriflunomide has been questioned [199], and testing is not currently routinely available in the UK.

We did not identify any data on breastmilk exposure to LEF, and no information is available in LactMed [192].

Recommendations for leflunomide in pregnancy and breastmilk exposure

i) LEF may not be a human teratogen but there remains insufficient evidence to support use at the time of conception or during pregnancy (GRADE 1B, SOA 98%).
ii) Women on LEF considering pregnancy should stop and undergo a standard cholestyramine washout procedure, and switch to alternative medication compatible with pregnancy (GRADE 1B, SOA 98.8%).
iii) If unintended conception occurs on LEF, the drug should be stopped immediately and a standard cholestyramine washout procedure given, with early referral

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to a foetal medicine department considered (GRADE 1B, SOA 99%).
iv) LEF is not recommended while breastfeeding (GRADE 1C, SOA 99.5%).

Azathioprine

Previously, we recommended that AZA is compatible with pregnancy at doses ≤2 mg/kg, with breastmilk exposure and with paternal exposure [1]. These recommendations were based on 28 studies [45, 50–52, 55, 61, 83, 88, 90, 92, 93, 95, 99, 101, 102, 107, 135, 172, 173, 203–211] in 738 AZA-exposed pregnancies, which included a wide range of diagnoses and concomitant medications, compared with 1121 disease-matched and 667 healthy controls. These data did not demonstrate an increased risk of miscarriage, preterm birth, low birth weight or congenital malformation due to AZA exposure in pregnancy.

We identified an additional nine studies of 3699 pregnancy exposures to AZA: six maternal studies [31, 78, 212–215] and three paternal studies [185, 187, 216]. Overall, the findings from maternal exposures ($n = 1019$) to AZA did not identify any adverse pregnancy outcomes. One study, reporting on AZA metabolism in 30 IBD pregnancies, measured active metabolites and found only 6-thioguanine nucleotide (6-TGN) but not 6-mercaptopurine (6-MP) in umbilical cord blood at delivery; no major teratogenicity was observed, although 60% of the infants had anaemia, which was suspected to be due to maternal thiopurine use [214]. Two of these studies extended follow-up to 3 months and nearly 10 years, without any adverse effects being reported. The majority of studies did not specify the mean/median dose of AZA utilized in the study populations, and there is no clear evidence regarding a dose limit. Use of AZA at an effective dose should be supported by monitoring of blood tests, following local guidelines.

Based on our previous evidence from 26 infants breastfed by mothers on AZA or 6-MP, minimal amounts of AZA were detected in breastmilk, and no adverse effects were identified [101, 209–211]. We did not identify any new studies of breastmilk exposure to AZA. LactMed states that avoiding breastfeeding for 4 h after maternal ingestion of AZA should markedly reduce the dose received by the infant in breastmilk [192]. In routine clinical practice, there is no concern in the management of solid organ transplant patients who breastfeed on this drug [217].

Recommendations for azathioprine in pregnancy and breastmilk exposure

i) AZA is compatible throughout pregnancy (GRADE 1B, SOA 100%).
ii) AZA is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Ciclosporin

An earlier consensus document reviewed evidence from >800 human pregnancies exposed to ciclosporin (CsA) [68]. Our previous search from 2005 onwards identified a further 13 studies/reports [43, 50, 51, 54, 88, 92, 93, 95, 101, 135, 136, 165, 218] of 98 pregnancies in patients with a variety of diseases and multiple concomitant medications who had been exposed to CsA at 2–6 mg/kg during pregnancy. Reports of increased rates of preterm delivery and low birth weight were confounded by maternal disease and concomitant medications, and there was no evidence of an increased malformation risk [1]. Comorbidities, such as hypertension, pre-eclampsia and gestational diabetes mellitus, were reported at higher incidences than the general population. Based upon this evidence, CsA was considered compatible with pregnancy at the lowest effective dose, with monitoring of blood pressure, blood glucose and renal function [68]. UKTIS draws a similar conclusion [171].

We identified an additional five studies of 550 pregnancy exposures [182, 185, 219–221]. Three studies reported on maternal exposure [182, 219, 220]. A cohort study of 240 SLE pregnancies, in whom 50% were exposed to CsA before and during the first trimester, increased the risk of pancytopenia and/or pre-eclampsia in maternal outcomes [182]. A single-centre experience of outcomes of pregnancy ($n = 117$) following liver transplantation did not find any difference between those on CsA ($n = 34$) compared with tacrolimus ($n = 81$), and so did not attribute these outcomes to medication [219]. A study of the efficacy and safety of CsA in 29 pregnancies of patients with systemic autoimmune diseases did not find an increased risk of maternal–foetal complications, and stated that it should be continued in patients who benefit from therapy [220].

Previously identified studies described small amounts of CsA in breastmilk and almost universally undetectable blood levels in infants [68, 218], without any adverse effects reported during breastmilk exposure. We found a further study that reported low transfer of CsA and its metabolites into the breastmilk of seven post-transplant mothers in the first two days post-partum, although this study was not designed to make a corresponding assessment of drug safety [221]. LactMed recommends that breastfed infants should be monitored if CsA is used during lactation, possibly with measurement of serum levels if there is a concern for toxicity [192]. In routine clinical practice, there is no concern in the management of solid organ transplant patients who breastfeed on this drug [217].

No additional studies of long-term follow-up were identified to those found previously on 10 infants exposed to CsA *in utero*, which reported no complications at 11–14 months [43, 54, 135].

Recommendations for ciclosporin in pregnancy and breastmilk exposure

i) CsA is compatible throughout pregnancy with monitoring of maternal blood pressure, renal function, blood glucose and drug levels (GRADE 1B, SOA 100%).
ii) CsA is compatible with breastmilk exposure (GRADE 2C, SOA 99.7%).

Tacrolimus

Based upon previous consensus [68, 222] and our previous review of six studies [92, 93, 99, 107, 116, 223] of 26 pregnancies exposed to tacrolimus and two breastmilk exposure studies [223, 224], tacrolimus was considered compatible with pregnancy and breastmilk exposure. There were complex confounding issues in many of these studies and, overall, no adverse outcomes were considered to be directly attributable to tacrolimus [1].

We found additional evidence from eight studies of 489 pregnancy exposures to tacrolimus [219, 225–231]. Studies

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of maternal outcomes, mostly from solid organ transplant recipients, reported varying incidences of adverse maternal-foetal outcomes, but these outcomes were confounded by transplant-associated comorbidities and concomitant immunosuppression, particularly MMF [219, 225, 227–231].

UKTIS concludes that the available data do not suggest an association between spontaneous miscarriage, congenital malformation or intrauterine death and exposure to tacrolimus during pregnancy, but data are limited and potentially confounded; therefore, an increased risk of these outcomes cannot be excluded [171].

Previously, we found studies reporting low levels of tacrolimus in umbilical cord blood and breastmilk in small numbers of breastfed infants without any adverse effects [223, 224]. These findings were confirmed in an additional study of 13 breastfed infants of mothers with SLE [225]. This study found concentrations of tacrolimus in the umbilical cord blood were lower than those in the maternal blood; the relative infant dose in breastfed infants of tacrolimus was <1%, and the level of tacrolimus in infant blood was below detectable limits. LactMed suggests that exclusively breastfed infants should be monitored [192]. In routine clinical practice, there is no concern in the management of solid organ transplant patients who breastfeed on this drug [217].

Recommendations for tacrolimus in pregnancy and breastmilk exposure

i) Tacrolimus is compatible throughout pregnancy with monitoring of maternal blood pressure, renal function, blood glucose and drug levels (GRADE 2B, SOA 100%).
ii) Tacrolimus is compatible with breastmilk exposure (GRADE 2C, SOA 99.8%).

Cyclophosphamide

CYC is a known human teratogen and is gonadotoxic in men and women [68]. Our previous findings from reports of predominantly first trimester use of CYC in nine pregnancies, revealed multiple adverse outcomes in mothers with severe maternal disease and multiple concomitant medications [102, 106, 111, 167, 168]. No maternal complications of CYC were reported. The nine pregnancies ended in two first trimester miscarriages, six healthy infants and one major congenital anomaly (Klippel–Feil syndrome). Follow-up to 87–90 months in four live births reported normal development in three children [102] and the single case of Klippel–Feil syndrome [111].

We found an additional study of pregnancies ($n = 11$) in women with multiple sclerosis who had been exposed to CYC prior to conception [232]; 10 women had a successful delivery [five preterm delivery and one small for gestational age (SGA)], while one underwent elective termination. It should be noted, however, that the time between the last dose of CYC and conception in this study was an average of 3.7 ± 1.5 years (range 0.33–5.9 years).

Although it did not meet our inclusion criteria, one case report analysed breastmilk levels of CYC in a women with multiple sclerosis [233]. CYC levels in breastmilk samples were measured after IV CYC at a dose of 2.8 g, with relatively low levels identified in the milk. The authors reported an average relative infant dose for a period of four days that varied from 4.7% at day 1 to 0.9% at day 4.

Recommendations for cyclophosphamide in pregnancy and breastmilk exposure

i) CYC is a known teratogen and gonadotoxic, and therefore should only be considered in pregnancy in cases of severe life/organ-threatening maternal disease when there is appreciable risk of maternal and foetal morbidity and mortality without this therapy (GRADE 1B, SOA 99.5%).
ii) CYC is not recommended while breastfeeding (GRADE 2C, SOA 100%).

Mycophenolate mofetil

MMF is a known teratogen and is recommended to be stopped at least 6 weeks before a planned pregnancy [68, 222]. It is rapidly absorbed following oral administration and hydrolysed to form the active ingredient, mycophenolic acid (MPA). This active metabolite has a mean apparent half-life of 17 h after a 1 g oral dose of MMF, and undergoes enterohepatic circulation, with a secondary plasma peak at 6–12 h after an oral or intravenous dose [234].

We previously reviewed data from 16 studies/reports [57, 60, 92, 95, 99, 113, 114, 116, 208, 235–241] of 90 pregnancies exposed to MMF, mostly from renal transplant patients in whom there was concomitant exposure to prednisolone and tacrolimus. Increased rates of premature delivery, low birth weight and major congenital malformations were reported, including malformations typical for the previously described MMF embryopathy (including cleft lip and/or palate, microtia with aural atresia, micrognathia and ocular anomalies) [1].

Our updated search found eight further studies of 934 pregnancy exposures to MMF: five maternal exposure studies [215, 242–245] and three paternal exposure studies [185, 246, 247]. The five studies of maternal exposure in pregnancies ($n = 714$) all reported increased risks of miscarriage and birth defects, with 351 foetal losses, eight stillbirths and 38 cases of congenital malformation [215, 242–245]. These studies were mostly of first trimester exposure, with three including second and third trimester exposures. One study, however, found that following discontinuation of MMF within 6 weeks of conception, outcomes including the rates of birth defects and miscarriages were similar to pregnancies not exposed to MMF [245].

UKTIS describes the increased risks of first trimester pregnancy loss, as well as major congenital anomalies, and states that women of childbearing potential who are prescribed MMF or MPA should be informed of the associated risks to the foetus and, therefore, the importance of adequate contraception. It notes that European Medicines Agency guidelines for male and female patients, published in October 2015 following a periodic safety update review, recommend additional measures to prevent foetal exposure to MMF and should be read prior to prescribing MMF [171].

As in our previous search, we did not identify any data on breastmilk exposure. Similarly, LactMed reports that no information is available on the excretion of MMF into breastmilk, and that a few infants have reportedly been breastfed during MMF therapy with no adverse effects reported [192].

We did not identify any additional long-term follow-up data to that previously found of one case of ‘small for age’ with otherwise normal development [57], and another study

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reporting on 3/6 exposed children (one with normal development, one who required hearing aids, and one who had motor and speech delay) [99].

Recommendations for mycophenolate mofetil in pregnancy and breastmilk exposure

i) MMF remains contraindicated during pregnancy, and should be avoided in women planning pregnancy or switched to a pregnancy-compatible alternative at least 6 weeks before attempting to conceive (GRADE 1B, SOA 100%).
ii) In cases of unintended conception, switch MMF to a pregnancy-compatible alternative and refer to local experts for further advice and risk assessment (GRADE 1B, SOA 100%).
iii) MMF is not recommended while breastfeeding (GRADE 2C, SOA 99.7%).

Intravenous immunoglobulin

IVIG is considered to be compatible with pregnancy and breastmilk exposure [68, 222]. Our previous review of data found 16 studies/reports [48, 49, 58, 82, 97, 110, 127, 128, 133, 248–254] of 336 pregnancies in which IVIG was used, mostly in APS or in the prevention of CHB in anti-Ro/La positive mothers. The studies identified were focused on therapeutic efficacy rather than the safety of IVIG; hence, all outcomes were confounded by use in patients with high-risk pregnancies and multiple concomitant medications. Overall, the number and type of maternal and foetal complications observed were compatible with known effects of the underlying maternal disease on pregnancy, rather than being specific to IVIG. The studies reviewed did not raise any new concerns to question the accepted safety of IVIG in pregnancy [1].

We identified two further studies of 67 exposures to IVIG to treat immune thrombocytopenia (ITP) in pregnancy [74, 79]. One study found that glucocorticoids increased the risk of maternal hypertension, while the addition of IVIG to corticosteroid regimes did not adversely affect pregnancy outcomes [79]. The other study found comparable benefits of IVIG compared with corticosteroids in treating ITP in pregnancy, compared with no treatment, and similar neonatal outcomes between the treatment groups [74]. UKTIS does not report on IVIG.

None of the studies we previously or recently identified addressed the use of IVIG in breastmilk exposure or with paternal exposure. LactMed states that immunoglobulin is a normal component of breastmilk, and data from two mothers indicate that IgG concentrations in milk are normal or higher, and IgM levels in milk are normal or lower, during IVIG therapy [192].

Recommendations for intravenous immunoglobulin in pregnancy and breastmilk exposure

i) IVIG is compatible with pregnancy (GRADE 1B, SOA 99.5%).
ii) IVIG is compatible with breastmilk exposure (GRADE 2C, SOA 100%).

Biologic DMARDs

Biological therapies are commonly used as second-line agents to treat various forms of IRDs. They are recombinant proteins, most commonly monoclonal IgG1 antibodies directed against specific targets, or fusion proteins containing the Fc portion of IgG1 joined to receptor-blocking proteins. The presence of the Fc region of IgG1 in most of these biologic drugs is required for their active placental transfer, which accelerates by active transport from the second trimester onwards. Biologic drugs are often given alongside other DMARDs, and decisions regarding continuation of treatment should be taken for each drug independently. Although the evidence base for biosimilar use in pregnancy and breastmilk exposure is more limited than for originator biologics, they would be expected to have comparable effects. Therefore, for pragmatic reasons, our recommendations are applicable to equivalent licensed biosimilars.

Five studies were identified that assessed the impact of biologic drugs as a whole on pregnancy outcomes [255–259]. These studies included a total of 379 pregnancies in women with autoimmune disease on predominantly anti-TNFα drugs, but also rituximab (RTX), abatacept (ABA), tocilizumab (TCZ), ustekinumab (UST) and anakinra. Separate birth outcomes for specific medications were not reported. Overall, the authors of these studies found no increased risk of miscarriage, stillbirth or congenital anomalies in biologic-exposed patients. One study that reported outcomes for 120 pregnancies in women with autoimmune diseases (predominantly RA and IBD) found a slightly increased risk of prematurity and a trend towards low birth weight in the biologic-exposed group compared with those not exposed [257]. However, once statistical modelling had been performed to correct for confounding by indication and proxies of unmeasured confounders, no association was found between biologic exposure and birth weight or gestational age. In addition, the same authors found that biologic use was not associated with an increased risk of serious infections in mothers, during postpartum, or in infants during the first year of life [256].

Anti-TNFα drugs

Five biologic agents that inhibit TNFα (TNFi) are currently licensed to treat IRDs: etanercept (ETA), infliximab (INF), adalimumab (ADA), golimumab (GOL) and certolizumab pegol (CZP). Three of these drugs (INF, ADA and GOL) are monoclonal IgG1 directed against TNFα, one (ETA) is a fusion protein of the TNF receptor joined to the Fc region of IgG1, while CZP is an antigen-binding fragment (Fab′) of a monoclonal anti-TNFα antibody which lacks the Fc region of IgG1 and has been conjugated with polyethylene glycol (PEG). These drugs have different half-lives, bioavailability and rates of placental transfer, which are relevant when considering their potential use in pregnancy.

Initial 2006/8 consensus recommendations advised avoidance of ETA, INF and ADA in pregnancy and breastfeeding due to a lack of evidence rather than evidence of harm [68, 222]. Previously, we reviewed outcome data from TNFi-exposed pregnancies ($n = 706$) of patients with predominantly IBD but also rheumatic disease and non-autoimmune-mediated recurrent spontaneous miscarriage, compared with ($n = 399$) disease and ($n = 170$) healthy control pregnancies [50, 52, 99, 100, 108, 109, 172, 173, 252, 260–279]. There were multiple confounders of concomitant therapies (including MTX, LEF

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and MMF) and active inflammatory disease. Overall, these studies did not describe an increased incidence of adverse effects upon miscarriage rates, pregnancy duration, birth weight, foetal death or congenital malformation that was attributable to ETA, INF, ADA or CZP. At that time, there was limited information on placental transfer, and no published studies of GOL in human pregnancy or breastmilk exposure.

TNFi exposure in pregnancy and with breastmilk exposure has been extensively studied since our last search. We identified an additional 50 studies, reporting 12 491 pregnancy exposures to TNFi, including INF ($n \geq 5377$), ADA ($n \geq 2797$), ETA ($n \geq 2210$), CZP ($n \geq 776$) and GOL ($n \geq 196$) [37, 255–259, 280–323]. Many studies reported combined outcomes for exposure to different TNFi agents. The majority of studies of maternal exposure did not report an increased risk of preterm birth, miscarriage, low birth weight or congenital malformations [37, 255, 257–259, 280–286, 288–291, 294, 296, 298–302, 304–308, 314, 316–318, 320–323].

Different adverse outcomes were reported in some studies, however. A study of ETA found that the proportion of infants with major birth defects was higher (9.4% *vs* 3.5%, respectively) in ETA-exposed pregnancies ($n = 370$) than in pregnancies of disease-matched, non-exposed women ($n = 164$) [287]; however, the lack of a specific pattern of birth defects and the expected minimal placental transfer of ETA in early pregnancy did not support the biologic plausibility of a drug-related effect. A study reporting a lower live birth rate in INF-exposed pregnancies ($n = 99$) in women with Crohn's disease considered their findings to be confounded by more severe disease in those patients exposed to INF and increased exposure to other immunosuppressive agents [293]. A population-based study of TNFi-exposed pregnancies ($n = 1027$) found increased risks of preterm birth, caesarean section and SGA babies in comparison with TNFi-unexposed pregnancies ($n = 9399$) [295]; however, the authors noted that these associations may have been related to underlying disease activity rather than agent-specific effects, due to diverse findings across disease groups.

A retrospective cohort study of TNFi-exposed pregnancies ($n = 1457$) in women with IBD found TNFi exposure to be an independent risk factor for maternal complications and infections when compared with TNFi-unexposed pregnancies ($n = 9818$) [303]. In this study, TNFi exposure did not associate with congenital malformations or an increased risk of infection in children during the first year of life. Furthermore, there was no difference in the risk of complications in women exposed to TNFi during the third trimester, relative to cessation before week 24, although disease relapses were more common in those stopping TNFi prior to the third trimester. A study of 4961 pregnant women with autoimmune inflammatory conditions found similar risks of serious infections in women taking steroids, csDMARDs or TNFi during pregnancy, but found that higher doses of steroids were an independent risk factor for serious infections in pregnancy [323].

A registry-based study from Denmark and Sweden reported a non-statistically significant higher risk of having children with birth defects in women with RA, AS, psoriatic arthritis (PsA), IBD or psoriasis who had received TNFi during pregnancy ($n = 683$), relative to women with chronic inflammatory disease but without TNFi exposure ($n = 21\,549$) [310]; however, the heterogeneity of observed birth defects went against a common aetiology. A prospective cohort study of TNFi pregnancy exposures ($n = 495$) in women with chronic inflammatory disease (RA, AS, PsA, psoriasis and IBD) found prenatal TNFi exposure to be associated with an increased risk of birth defects without a distinct pattern of malformations, when compared with non-disease-matched, TNFi-unexposed controls ($n = 1532$) [312]. An increased risk of preterm births and reduced birth weight, but not spontaneous miscarriage, was also noted. The authors concluded that, although TNFi may carry a risk of adverse pregnancy outcomes of moderate clinical relevance, they may remain a treatment option, considering the impact of inadequately controlled disease on the mother and unborn child.

A small number of studies specifically compared risks between TNFi agents. In one study, INF was found to be associated with a greater risk for preterm births relative to ETA, and a higher prevalence of severely SGA babies relative to ETA and ADA, in pregnant women with RA, AS, PsA or psoriasis. In IBD, however, the risk of preterm births and SGA babies did not differ between INF and ADA [295]. In a study of individual safety reports in pregnant IBD patients exposed to TNFi ($n = 783$), the odds for maternal or foetal adverse events were found to be lower for CZP monotherapy, but not for INF or ADA monotherapy, when compared with an aminosalicylate monotherapy comparator in multi-level regression models [316]. In another study, the risk of birth defects did not differ significantly between ADA, INF or ETA-exposed women with chronic inflammatory diseases [310].

Several studies specifically compared outcomes for pregnancies exposed to TNFi during late *vs* early trimesters [37, 280–282, 284, 289, 291, 292, 295–297, 303, 305, 308, 309, 317], the majority of which reported no significant concerns with late trimester exposure. In a study of INF-exposed pregnancies ($n = 1850$) in women with IBD, RA, AS, PsA and psoriasis, frequencies of congenital abnormalities and other adverse birth and infant outcomes (including neonatal infections) were similar when comparing first and third trimester exposure [291]. In a study comparing early discontinuation of INF (>90 days before delivery; $n = 68$) to late discontinuation (<90 days before delivery; $n = 318$) in pregnancies of women with IBD, early discontinuation was associated with increased disease flares, more steroid usage and more preterm births than late discontinuation [292]. Rates of other adverse outcomes, including congenital malformations and infant respiratory infections, were similar between these groups. A further study of TNFi-exposed pregnancies ($n = 153$) in women with IBD reported that continuation of TNFi after gestational week 30, relative to cessation before week 30, was independently associated with modestly lower birth weights in multivariate regression models after adjustment for disease activity, but not other adverse infant outcomes [297].

Different rates of placental transfer of TNFi and timing of drug exposure in the second and/or third trimester of pregnancy influenced previous advice regarding avoidance of live vaccines in the first 7 months of life. Previously, a small cohort study found CZP (a PEGylated Fab' fragment, lacking the Fc region) to have minimal rates of placental transfer compared with INF and ADA [270], and two case reports demonstrated very low rates of placental transfer of ETA administered throughout pregnancy [108, 274]. Therefore, previous recommendations described discontinuation of ADA and ETA at the end of the second trimester to ensure negligible or no drug is detectable in cord blood at delivery. For INF, due to its prolonged bioavailability and higher rate of placental transfer, it

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was recommended to be stopped earlier in pregnancy (at 16 weeks) for it to be undetectable in cord blood at delivery.

Since the last guideline, we found increased data demonstrating different rates of placental transfer of TNFi [283, 285, 302, 308, 309]. In a study of pregnant women with IBD exposed to INF ($n = 44$) or ADA ($n = 36$), the median time to drug clearance was 4 months for ADA and 7 months for INF [308]. In this study, continuation of TNFi in the third trimester did not increase the risk of childhood infection, relative to discontinuation before the third trimester. In a prospective study of ADA ($n = 58$) and INF-exposed pregnancies ($n = 73$) in women with IBD, cord blood samples showed significantly higher levels of INF than ADA at birth [302]. In this study, placental transfer of INF increased exponentially over the third trimester, while ADA transportation was limited and increased in a linear fashion. Maternal and birth outcomes were comparable between these groups, as were one-year infant health outcomes, including infection and adverse reactions to vaccinations. A study of infants ($n = 14$) with third trimester maternal exposure to CZP found minimal rates of placental transfer, supporting continuation of this treatment during pregnancy [283]. Recent data, published after our literature search and highlighted by UCB Pharma during public consultation, reported no signal for adverse pregnancy outcomes following maternal CZP exposure in a large ($n = 1425$) cohort [324].

UKTIS reports that studies that investigate the use of TNFi (ADA, CZP, ETA and INF only) during pregnancy have not found an overall increased risk of congenital malformation for these therapies as a class; there is also no compelling evidence of an increased risk for spontaneous miscarriage, intrauterine death or adverse neurodevelopmental outcomes; however, data are currently too limited to exclude adverse effects on the foetus. LBW and preterm birth have been associated with *in-utero* TNFi exposure in some studies but are confounded by maternal disease. UKTIS also states that there are theoretical concerns that the use of immunosuppressant antibodies, which actively cross the placenta, may result in neonatal or infant immunosuppression and increase the risk of infection; therefore, a delay is advised in administration of live vaccines to infants of: 5 months after last dose of ADA; 16 weeks after last dose of ETA; and until 6 months of age after *in-utero* INF. In contrast, as CZP is minimally transferred across the placenta, it is unlikely that infants born to women who used CZP in pregnancy would experience sufficient levels of TNFα inhibition to significantly inhibit their immune response [171].

Previously, we found case reports and case series reporting detection of ADA in breastmilk but not in infant serum [269], and detection of ETA and INF in breastmilk in some [108, 267, 273, 274] but not all studies [265], with no adverse effects detectable in any of these breastfed infants. We found nine additional studies of TNFi reporting on 133 breastmilk exposures [283, 285, 300, 307, 308, 317, 319, 325, 326]. Overall, these studies did not find any adverse effects of TNFi. A study of mothers ($n = 17$) breastfeeding while taking CZP found minimal transfer of this drug into breastmilk [325]. Another study reported low or undetectable concentrations of INF, ADA, CZP, GOL and UST in 72 breastmilk samples [326]. In this study, breastfed infants on biologics ($n = 243$), thiopurines ($n = 102$) or combination therapy ($n = 67$) were found to have similar risks of infection and rates of milestone achievement compared with infants unexposed to these drugs via breastmilk or not breastfed. LactMed states that: CZP is excreted into breastmilk in some, but not all, women in small amounts; INF is usually either not detectable in breastmilk or detectable at very low levels; ETA, ADA and GOL are minimally excreted into breastmilk, with all TNFi being predicted to be poorly absorbed by the infant due to large molecular weight of each drug [192]. While some evidence suggests that IgG antibodies may not be digested by the gut in the early neonatal period [327, 328], other studies demonstrate marked digestion of IgG by the infant gut [329, 330].

Previously, we found long-term follow-up data in children exposed *in utero* to ETA [108, 266, 270, 272–274], ADA [269] and CZP [270]. We found an additional 16 studies reporting long-term follow-up data after exposure to TNFi [256, 291, 292, 299–303, 307–309, 317, 319–322]. In one study, 196 children with intrauterine exposure to TNFi (ADA, $n = 81$; INF, $n = 115$) for maternal IBD were followed up for 5 years, finding no association with long-term adverse health outcomes (including childhood infections and vaccination adverse reactions) when compared with TNFi-unexposed controls [296]. This study included women continuing TNFi during the third trimester, where no increased risk of infection was noted in their offspring. In a retrospective cohort study of children ($n = 388$) exposed to TNFi (ADA, $n = 164$; INF, $n = 223$; CZP, $n = 1$) *in utero* for maternal IBD, the incidence of severe infections was similar to TNFi-unexposed children of IBD mothers after median follow-up of 5 years [301]. Similarly, in another study, the risk of serious or opportunistic infections during the first year of life in live-born infants ($n = 229$) exposed to ADA during pregnancy in women with RA or IBD was not significantly different to disease-matched, non-exposed controls and healthy controls [281]. In this study, the risk of infection remained similar when restricting to infants exposed to ADA during the third trimester. Two additional studies, which were not included in our final analysis because they did not report primarily on pregnancy or breastmilk exposure outcomes, described infections in the first 3 years of life in children after *in-utero* exposure to TNFi (predominantly ETA, ADA and INF) and/or csDMARDs for IRDs, psoriasis and IBD. One study of 493 children exposed *in utero* to TNFi reported an increased risk of some site-specific infections but not other adverse outcomes within the first year of life only [331]. The other study of 1027 children demonstrated a slightly increased risk of paediatric infections associated with both TNFi and csDMARDs in the first and second year after birth; however, the authors noted that this association was present regardless of third trimester exposure and could also have been confounded by disease severity [332].

Studies of vaccine safety and efficacy were not specifically sought through our systematic literature search but are relevant to consider, because most guidance recommends avoidance of live vaccines up to 6–12 months post-partum in infants exposed to bDMARDs in the second/third trimester [1, 333]. This advice is heavily influenced by the finding that placental transfer of bDMARDs can lead to persistence of drug levels by up to 12 months following *in-utero* exposure, with a median clearance time of 6 months and longest clearance times for INF. In addition, a fatal case of disseminated TB-like disease had been reported in a 4-month-old infant who had received Bacille Calmette et Guerin (BCG) vaccination following *in-utero* exposure to INF [334]. This guidance

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impacts on rotavirus vaccination and, if indicated, the BCG vaccine, while the measles, mumps and rubella (MMR) vaccine (typically given at 12 months) is not affected. These restrictions significantly impact on rotavirus only, since the BCG vaccine may easily be deferred to be given later in life, while the rotavirus course of vaccination must be completed by 24 weeks of age due to risk of intussusception [335]. Currently, the restrictions may be avoided by discontinuing TNFi in the second or early third trimester, several half-lives prior to delivery.

Rotavirus continues to be a major cause of acute gastroenteritis in young children and has been estimated to result in >500 000 deaths and 2.4 million hospital admissions worldwide [336]. The rotavirus vaccine is over 85% effective at protecting against severe rotavirus gastroenteritis in the first two years of life [335]. Although current UK guidance recommends avoidance of rotavirus vaccination in infants of mothers exposed to biologics during pregnancy [337], it refers readers to the green book [335]. This text states that, although the vaccine is a live attenuated virus, with the exception of severe combined immunodeficiency (SCID), the benefit from vaccination may exceed risk in other forms of immunosuppression [335].

There are increasing reports of the safe use of rotavirus vaccination in infants following perinatal exposure to bDMARDs, including INF. A systematic review described cohort studies and case reports of infants ($n = 54$) of mothers who received antenatal bDMARDs (mostly TNFi, including INF) who then received rotavirus vaccine without significant adverse effects [336]. The authors of that review recommended that otherwise healthy newborns with a history of perinatal exposure to bDMARDS should receive rotavirus vaccinations as per the recommended schedule, while the BCG vaccine should be withheld in the first year of life. Not all consensus review articles have reached the same conclusion, however, with some recommending avoidance of both rotavirus and BCG vaccinations in infants exposed to bDMARDs *in utero* in the first 6 months of life unless levels of biological drugs are undetectable [338], or avoidance of live vaccines until 6–12 months of age in infants exposed to biologics that may cross the placenta at clinically significant levels [339].

A systematic review published in abstract form after our search date evaluated vaccine safety in infants exposed to bDMARDs or tsDMARDs in pregnancy [340]. It identified *in-utero* exposures to ADA ($n = 326$), CZP ($n = 18$), ETA ($n = 1$), INF ($n = 408$), GOL ($n = 1$), RTX ($n = 1$), TCZ ($n = 3$), UST ($n = 1$) and no tsDMARD exposures in mostly IBD ($n = 849$) pregnancies. Infant vaccination included: BCG ($n = 111$) and/or rotavirus ($n = 48$) in the first year of life (many <6 months); and MMR at 12 months ($n = 590$), 6–9 months ($n = 12$) and at 1, 2 or 4 months ($n = 3$). Adverse events with BCG vaccination included one death, two large local skin reactions, and one infant with axillary lymphadenopathy. A freedom of information request to the MHRA revealed four further suspected fatal BCG infections in infants exposed to TNFi *in utero* (INF, $n = 2$; ADA, $n = 1$; and unspecified TNFi, $n = 1$). Adverse effects noted in infants given rotavirus vaccination were mild and at similar frequency to those in biologic-unexposed infants. No complications were reported with MMR vaccination. Overall, the most evidence of clinically harmful effects was found after administration of BCG to infants <3 months of age and after *in-utero* exposure to INF. In contrast, outcomes following rotavirus (mostly <6 months) and MMR (mostly at a year) vaccinations were reassuring. Notably, disseminated rotavirus infection has not been reported.

Other systematic reviews have also evaluated vaccine efficacy, and report adequate vaccination response (measured by antibody levels) following non-live vaccination in infants exposed to TNFi [336], although there are conflicting reports, with low antibody responses to the Haemophilus influenzae type-B vaccine reported in some infants exposed to INF or ADA [338].

Although our literature search did not assess evidence relating to the peri-operative use of TNFi or other bDMARDs (for example, in the context of caesarean sections), relevant guidance can be found in other BSR guidelines [341].

Recommendations for anti-TNFα medications in pregnancy and breastmilk exposure

i) Women with no/low disease activity established on a TNFi with known placental transfer (INF, ADA, GOL) do not need to be switched to an alternative TNFi with established minimal placental transfer (CZP) either before or during pregnancy (GRADE 1B, SOA 100%).
ii) CZP is compatible with all three trimesters of pregnancy, has no to minimal placental transfer compared with other TNFi, and does not require any alteration to the infant vaccination schedule (GRADE 1B, SOA 100%).
iii) Women considered to have low risk of disease flare on withdrawal of TNFi in pregnancy could stop INF at 20 weeks, ADA and GOL at 28 weeks, and ETA at 32 weeks so that a full-term infant can have a normal vaccination schedule, with rotavirus vaccination at 8 weeks as per the UK schedule (GRADE 1B, SOA 99.5%).
iv) INF, ADA, ETA or GOL may be continued throughout pregnancy to maintain maternal disease control; in these circumstances, live vaccines should be avoided in infants until they are 6 months of age (GRADE 1B, SOA 100%).
v) If a TNFi is stopped in pregnancy, it can be restarted as soon as practical post-partum in the absence of infections or surgical complications, regardless of breastfeeding status, to ensure control of maternal disease (GRADE 1C, SOA 100%).
vi) TNFi are compatible with breastmilk exposure (GRADE 1C, SOA 100%).

Other biologic DMARDs (non-TNFi)

Data relating to non-TNFi biologic use in pregnancy remain scarce, and in this guideline updated case reports and small case series were excluded for consistency. A recent systematic review summarized all available data (including case reports) on non-TNFi bDMARDs and tsDMARDs and did not identify any adverse safety signals [342].

Rituximab

Previously, we found insufficient evidence to be confident that RTX is compatible with pregnancy and recommended it should be stopped 6 months before conception, although there were no direct reports of teratogenicity and only second/third trimester exposure was associated with neonatal B-cell

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depletion. RTX is a monoclonal IgG1 that actively crosses the placenta from 16 weeks of pregnancy onwards. Previously, we found eight studies [50, 343–349] on 173 RTX-exposed pregnancies that met our inclusion criteria. Overall, these studies reported reassuring pregnancy outcomes, but found low B cells at birth in infants exposed to RTX in the second/third trimester, no human breastmilk exposure studies were identified [1].

We identified five further studies of 143 RTX pregnancy exposures [350–354] in addition to eight exposures in studies that reported on combined outcomes of multiple biologic-exposed pregnancies (see 'Biologic DMARDs' above). Four studies ($n = 135$) of mostly pre-conception or first trimester maternal exposure did not report an increased risk of preterm birth, miscarriage, LBW or congenital anomaly [350–352, 354]. An additional cohort study of eight mothers treated with one to four cycles of RTX during pregnancy ($n = 6$ for diffuse large B-cell lymphoma; $n = 2$ for SLE) found a high rate of preterm birth and intrauterine infections, but noted the potential for confounding by the underlying disease and concomitant medications [353].

UKTIS reports that there is insufficient evidence to assess whether the risk for spontaneous miscarriage, congenital malformation, birth weight, intrauterine death or adverse neurodevelopmental outcomes is increased following exposure to RTX *in utero*. Due to a lack of data on the effects of RTX on the neonatal/infant immune system, it recommends delaying administration of live vaccines following *in-utero* exposure to RTX, although no specific timescale is given [171].

There were three studies of breastmilk exposure ($n = 23$) to RTX [352, 354, 355]. One study detected minimal transfer of RTX into the breastmilk of nine breastfeeding mothers, with a relative infant dose of rituximab well below theoretically acceptable levels (<0.4%) [355]. No adverse effects attributable to RTX exposure were reported in the breastfed infants, and the drug was considered to have an acceptable benefit-to-risk ratio, supporting both maternal treatment and breastmilk exposure. LactMed states that the amount of RTX in breastmilk is very low and absorption is unlikely because it is a protein with a high molecular weight that is likely to be partially destroyed in the infant's gastrointestinal tract; thus, absorption by the infant is probably minimal [192].

Vaccine efficacy after prenatal exposure to RTX is much less studied, and systematic reviews have identified adequate non-live vaccination outcomes from 5/6 RTX-exposed infants, with low immunity to diphtheria detected in one 11-month-old infant exposed to RTX at conception [336, 338].

Recommendations for rituximab in pregnancy and breastmilk exposure

i) Limited evidence has not shown RTX to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception (GRADE 2C, SOA 99.3%).
ii) RTX may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.7%).
iii) If RTX is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 98.7%).
iv) Based on limited evidence, maternal treatment with RTX is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Interleukin-6 inhibitors

Tocilizumab

Due to insufficient data, we previously recommended that TCZ be stopped at least three months pre-conception, but that unintentional exposure early in the first trimester is unlikely to be harmful due to its IgG1 structure. This limited data came from outcomes of 33 pregnancies in 32 patients, published in abstract form [356]. We identified three further studies of 365 pregnancy exposures to TCZ [357–359] in addition to four exposures in the papers described above which reported combined outcomes of multiple biologic-exposed pregnancies (see 'DMARDs' above). These studies of mainly first trimester exposure did not find increased rates of congenital abnormalities in patients with rheumatic disease. Two studies commented on a higher than background rate of spontaneous miscarriage [357, 359], and could not exclude an effect on birth weight and risk of prematurity, while acknowledging potential confounding factors. For example, stopping effective treatment early in pregnancy could destabilize the rheumatic disease, with adverse consequences for the pregnancy.

UKTIS notes a small number of studies lacking comparator groups that are confounded by maternal disease, and states that there is currently no compelling evidence that TCZ is teratogenic or fetotoxic. Due to lack of data on effects on the neonatal/infant immune system, it recommends that live vaccines are avoided until the infant is 6 months of age [171].

One study of $n = 2$ breastmilk exposure to TCZ did not report any adverse effects attributable to the drug [360]. Saito *et al.* have described a total of four cases of babies exposed to TCZ via breastmilk with no complications in the infants (three publications which did not meet our inclusion criteria) [360–362]. Concentrations of TCZ were measured in the breastmilk in these studies and two additional cases reports, with no clinical adverse effects reported [363, 364]. Levels in the breastmilk were found to peak on day three following the infusion [362], but were significantly lower than the corresponding maternal serum concentrations in all of these cases, ranging from 11% in colostrum [364], down to as low as 1:2000 [360, 363].

Sarilumab

No papers were found that met our inclusion criteria. Sanofi provided data on 13 patients who became pregnant in the sarilumab and DMARD long-term safety population, of whom seven had a miscarriage [365]. In addition, two male patients fathered two healthy children.

Recommendations for IL-6 inhibitors in pregnancy and breastmilk exposure

i) Limited evidence has not shown IL-6 inhibitors (IL-6i) to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.7%).
ii) IL-6i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 100%).

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iii) If IL-6i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%).
iv) Based on limited evidence, maternal treatment with IL-6i is compatible with breastmilk exposure (GRADE 2C, SOA 100%).

Interleukin-1 inhibitors

Anakinra

Anakinra is a recombinant form of human interleukin-1 receptor antagonist (IL-1Ra) with a high molecular weight which was not found to cross *ex-vivo* full-term human placentae [366]. Previously, there was insufficient information evidence on which to base a recommendation for anakinra in pregnancy, but unintentional exposure in the first trimester was considered unlikely to be harmful [1]. This limited evidence came from reports on five pregnancies in three studies/reports, with no evidence of harm [50, 367, 368].

Subsequently, we identified four studies of 43 pregnancy exposures to anakinra [369–372], in addition to one exposure in the papers described above which reported combined outcomes of multiple biologic-exposed pregnancies (see 'Biologic DMARDs' above). These exposures were mostly in patients with periodic fevers and severe maternal disease. Overall, outcomes were reassuring, although two congenital renal anomalies and two cases of oligohydramnios (which can be linked to foetal renal anomalies) were reported [369, 371, 372]. It was unclear, however, whether the renal abnormalities were associated with antenatal anakinra use or maternal hyperthermia or both. Given the significant beneficial effects of anakinra in suppressing maternal disease with limited pregnancy-compatible options, it was considered a safe alternative in managing disease in women with periodic fever in pregnancy. UKTIS does not report on anakinra.

Two studies of $n = 12$ breastmilk exposures to anakinra did not report any adverse effects attributable to the drug [369, 371]. LactMed states that IL-1Ra is a normal component of human milk, possibly as an anti-inflammatory agent, and that several infants have been breastfed during maternal anakinra therapy with no obvious adverse effects. If anakinra is required by the mother, it is not a reason to discontinue breastfeeding [192].

Canakinumab

Canakinumab is a human monoclonal antibody to IL-1. There is, therefore, the potential for active transport across the placenta from the second trimester onwards.

One paper reporting canakinumab use from pre-conception in eight pregnancies (stopped during first trimester in 5/8 pregnancies) met our inclusion criteria [369]. There were seven live births, all of whom were healthy, full term and normal birth weight. One mother with refractory Cogan syndrome had an early miscarriage at 6 weeks (after a miscarriage the previous year while on anakinra).

In addition, Novartis supplied information from analyses of the Novartis Global Safety Database, which included 76 maternal and nine paternal exposures [373]. There were 47 known pregnancy outcomes, with 27 healthy newborns, one preterm birth (with meconium staining not thought likely to be related to canakinumab exposure), nine spontaneous miscarriages (including two miscarriages related to paternal exposure in one father) and three elective terminations. Seven other adverse events were reported: one case of congenital pyelocaliectasis following paternal exposure to canakinumab; one case of congenital musculoskeletal abnormality following maternal exposure, with insufficient data on other contributory factors; one case of inherited genetic disease with neonatal RSV infection and pyrexia following infant vaccinations; and four adverse events very unlikely to relate to canakinumab exposure (one newborn non-serious hypotension and three cases of likely inherited disease: Muckle–Wells syndrome and CAPS).

One cohort study reported breastmilk exposure in four infants whose mothers were prescribed regular canakinumab, with no reported serious infections or developmental abnormalities [369].

Recommendations for IL-1 inhibitors in pregnancy and breastmilk exposure

i) Limited evidence has not shown IL-1 inhibitors (IL-1i) to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.8%).
ii) IL-1i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 100%).
iii) If IL-1i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%).
iv) Based on limited evidence, maternal treatment with IL-1i is compatible with breastmilk exposure (GRADE 2C, SOA 100%).

Abatacept

ABA is a fusion protein containing the Fc region of IgG1 fused to the extracellular domain of CTLA-4; therefore, it is able to cross the placental barrier from approximately week 16. Previously, there was insufficient data to recommend ABA in pregnancy, but unintentional exposure early in the first trimester was considered unlikely to be harmful [1]. This conclusion was based on reports from 11 pregnancy exposures (and a further eight exposures reported in abstract form only), many of which were confounded by concomitant MTX [175, 349, 374].

We identified two further studies of at least 196 pregnancy exposures to ABA (with some overlap of data) [375, 376], in addition to three exposures in the papers described above which reported combined outcomes of multiple biologic-exposed pregnancies (see 'Biologic DMARDs' above). The data from these studies did not suggest an increased risk of adverse pregnancy outcomes with ABA, and many of the congenital abnormalities were considered by the authors to be associated with concomitant use of other teratogenic DMARDs. The apparently high rate of spontaneous miscarriage (total $\geq$48/184) is difficult to interpret due to confounding by indication and other medications such as MTX, as well as detection bias of early miscarriages during the close monitoring of clinical trials [375]. The authors concluded that ABA should only be used during pregnancy if the benefit to the mother justifies potential risk to the foetus. UKTIS does not report on ABA.

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Although it did not meet our inclusion criteria, we identified one case report of breastmilk exposure to ABA, with no adverse effects, in which ABA was secreted into breastmilk at levels 1/200–1/300 of those in serum [377]. LactMed describes one case report that reported concentrations of ABA in milk were very low and did not appear to affect the breastfed infant, concluding that if ABA is required by the mother, it is not a reason to discontinue breastfeeding, although alternative drugs may be preferred [192].

Recommendations for abatacept in pregnancy and breastmilk exposure

i) Limited evidence has not shown ABA to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%).
ii) ABA may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.3%).
iii) If ABA is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%).
iv) Based on limited evidence, maternal treatment with ABA is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Belimumab

Belimumab (BEL) is a fully humanized monoclonal IgG1 that inhibits B-cell activating factor. Previously, our systematic search did not identify any publications that met our search criteria on use of BEL in human pregnancy, although we found reference to pregnancy outcomes from placebo-controlled, phase 2 and 3 studies in 83 SLE pregnancies [378], and BEL pregnancy registry data describing known outcomes from 118 SLE pregnancies [379]. Overall, these studies did not identify any pattern of adverse effects in pregnancy directly attributable to BEL.

We subsequently identified one study of 66 BEL pregnancy exposures [380]. Total foetal losses in BEL-treated subjects were similar to background estimates in SLE patients (~25%), although data remain limited. Another six studies, which did not meet our search criteria [381–386], reported an additional 124 pregnancies exposed to BEL. There was only one reported congenital abnormality: a case report of mild Ebstein's anomaly in a baby following successful control of SLE (with previous lupus nephritis and APS, previously only controlled on MMF) [381]. Two case series (26 pregnancy exposures) reported preterm delivery in 12/22 live births, with six babies being SGA [385, 386]. However, these cohorts included patients with complex rheumatic disease (SLE and APS), including some patients with previous lupus nephritis and active disease at conception [385], and a high average maternal age and rate of previous pregnancy losses [386]. Both authors concluded that, while careful consideration and further research is required, BEL could be a reasonable treatment option for patients with SLE requiring treatment in pregnancy. UKTIS does not report on BEL.

Although they did not meet our inclusion criteria, we identified two cases of breastmilk exposure while on BEL [381, 382]. No neonatal outcomes, adverse or otherwise, were reported in one case [381]. In the other case, there were no adverse effects, and BEL was secreted into breastmilk at levels 1/200–1/500 of those in serum [382]. LactMed states that, based on preliminary information that BEL levels in breastmilk are very low and infant absorption is probably minimal, if BEL is required by the mother, it is not a reason to discontinue breastfeeding, although caution is required, especially while nursing a newborn or preterm infant [192].

Recommendations for belimumab in pregnancy and breastmilk exposure

i) Limited evidence has not shown BEL to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%).
ii) BEL may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99.5%).
iii) If BEL is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 98.8%).
iv) Based on limited evidence, maternal treatment with BEL is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Interleukin-17 inhibitors

Interleukin-17 inhibitors (IL-17i) were not in general use and so not considered in our previous search. Secukinumab has an IgG1 structure, which may theoretically suggest increased transplacental transfer compared with the IgG4 structure of ixekizumab.

We found three studies of mostly first trimester pregnancy exposures to secukinumab ($n = 244$) and ixekizumab ($n = 18$) [387–389]. The authors did not report any increased incidence of adverse outcomes directly attributable to the drugs, although information, particularly for ixekizumab, remains very limited.

In addition, Novartis provided data from a search of their Global Safety Database, relating to 298 reports of maternal pregnancy exposures and 90 paternal exposures to secukinumab, mostly during the first trimester [390]. No outcome data were provided, but analysis within Novartis did not reveal any new safety information. UKTIS does not report on these drugs.

There were no data on breastmilk exposure to IL-17i identified in our search or in LactMed. Data provided from the Novartis Global Safety Database identified six breastmilk exposures to secukinumab, including one report of newborn pyrexia during breastfeeding [390]. The data in all cases were too limited to draw conclusions, but no new safety concerns were inferred.

Recommendations for interleukin-17 inhibitors in pregnancy and breastmilk exposure

i) Limited evidence has not shown IL-17i to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy.

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Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%).

ii) IL-17i may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 99%).

iii) If IL-17i are used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%).

iv) Based on limited evidence, maternal treatment with IL-17i is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Interleukin-12/23 inhibitors

UST is an interleukin-12/23 inhibitor (IL-12/23i) with an IgG1 structure. UST was not in general use and not considered in our previous search. We found three studies of mostly first and second trimester pregnancy exposures to UST ($n = 517$) for maternal psoriasis, PsA and IBD [391–393]. Overall, these data showed that the rates of live births, spontaneous miscarriages and congenital anomalies were consistent with the general population and TNFi-exposed pregnancies.

Similarly, UKTIS did not identify any specific drug-related risk but was unable to provide a reliable evidence-based evaluation of risk due to limited information [171].

Although they did not meet our inclusion criteria, we identified two reports of exposure to UST during breastmilk exposure [326, 394]. In one case report, the trough level of UST in breastmilk after restarting this drug post-partum in a Crohn's disease patient was initially in the same range as the corresponding serum trough level, and then decreased during maintenance therapy [394]. In another study assessing breastfeeding mothers taking a range of biologic medication for IBD, UST was detected at low levels in 4/6 mothers taking this medication [326]. Overall, in this study, breastfed infants of mothers on biologics were found to have similar risks of infection and rates of milestone achievement compared with non-breastfed infants or infants unexposed to these drugs. LactMed states that UST is either not detectable or found at very low levels in breastmilk and infant absorption is probably minimal; as such, if UST is required by the mother, it is not a reason to discontinue breastfeeding, although caution is required especially while nursing a newborn or preterm infant [192].

Recommendations for interleukin-12/23 inhibitors in pregnancy and breastmilk exposure

i) Limited evidence has not shown UST to be teratogenic; however, there remains insufficient evidence to be confident that it is compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful (GRADE 2C, SOA 99.3%).

ii) UST may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable (GRADE 2C, SOA 98.8%).

iii) If UST is used to treat severe maternal disease in the third trimester, it is currently recommended to avoid all live vaccines in the infant vaccination schedule until 6 months of age (GRADE 2C, SOA 99.3%).

iv) Based on limited evidence, maternal treatment with UST is compatible with breastmilk exposure (GRADE 2C, SOA 99.5%).

Anifrolumab

Anifrolumab is a fully human, IgG1κ monoclonal antibody to type I interferon receptor subunit 1. Although it is not currently licensed for use in the UK, anifrolumab is approved for use in other countries, including FDA approval to treat moderate-to-severe SLE in the USA [395]. Although there is no published evidence on the use of this drug in pregnancy, breastmilk or paternal exposure, further information was provided by AstraZeneca on data from completed trials. Despite the mandatory contraception use in anifrolumab clinical trials, pregnancies have been reported in 20 SLE patients receiving anifrolumab in studies completed by December 2021. Patients who became pregnant during studies had to immediately discontinue the investigational product. No anifrolumab-associated congenital abnormalities or anifrolumab-associated adverse events have been observed in the clinical trials. Current data on anifrolumab pregnancy exposure are insufficient to inform about potential drug-related risks and therefore post-authorisation pregnancy studies are planned.

UKTIS does not report on anifrolumab. Although there is no information regarding breastmilk exposure to anifrolumab, LactMed states that due to its large molecular weight, the amount in milk is likely to be very low, and it is also likely to be partially destroyed in the infant's gastrointestinal tract with minimal absorption by the infant [192]. Based on this limited evidence, we have not made any recommendations on this drug.

Targeted synthetic DMARDs

Data relating to tsDMARD use in pregnancy remain scarce, and in this guideline, updated case reports and small case series were excluded for consistency. A recent systematic review summarized all available data including case reports and raised no additional safety concerns [342]. No studies were found relating to apremilast use in pregnancy, and therefore we were unable to make any recommendations.

JAK inhibitors

Tofacitinib (TOF), baricitinib (BAR) and upadacitinib (UPA) are oral Janus kinase inhibitors (JAKi) which were not in general use and so not considered in our previous search. They are small molecule inhibitors of low molecular weight which could theoretically cross the placenta.

JAKi have a short half-life (~3 h for TOF), although biological changes can persist for longer (for example, dose-dependent reductions in NK cells and CRP do not appear to reverse before 2 weeks after discontinuation) [396].

We identified three published reports of pregnancies during RCTs and post-marketing surveillance reports for TOF, but due to probable overlap, only the later 2018 paper was included (further updates were published in abstract form in 2020) [397–399]. This included 116 pregnancy exposures to TOF, with the known reported outcomes including 15/72 first trimester miscarriages, and major malformations in 2/44 live births (one pulmonary valve stenosis and one ventricular septal defect), which was in line with background risks in the general population [397].

Pfizer medical information supplied further details on pregnancies reported during the TOF clinical trials programmes

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[400]. The RA and psoriasis trials included a total of 60 maternal exposures during the first trimester with 51 known outcomes, with concomitant MTX use either before or during pregnancy in at least 19 of these cases [399]. There were 28 healthy newborns, two premature infants, and one congenital malformation where the mother was also taking losartan. In these trials, there were nine spontaneous miscarriages, nine medical terminations, and one elective termination. In the ulcerative colitis (UC) clinical trial programmes, there were 15 maternal exposures with 13 known outcomes (nine healthy newborns, two spontaneous miscarriages and two medical terminations) [397, 398]. In the PsA programmes, there were a further four maternal and three paternal exposures with six known outcomes (three healthy newborns, two spontaneous miscarriages and one medical termination) [397]. Post-marketing reports up to 2017 were included in the analysis by Mahadevan *et al.* with 42 (predominantly first trimester) maternal exposures and three paternal exposures, with only 12 known outcomes (seven healthy newborns, one congenital malformation, three spontaneous miscarriages and one medical termination) [397].

Although not eligible for inclusion, we found one case report of an RA pregnancy exposed to BAR from pre-conception up to 17 weeks gestation, with a healthy infant delivered at 38 weeks gestation by caesarean section [401]. In addition, Eli Lilly provided data on 36 maternal pregnancies during the BAR clinical trials programme, with 25 known outcomes (trimester and duration unspecified) [402]. Many were taking concomitant medications, including MTX ($n = 14$). Outcomes included 13 healthy newborns (including three born preterm), seven spontaneous miscarriages (with MTX exposure in six of these), and five elective terminations. In addition, there have been 22 post-marketing reports of pregnancy exposures to BAR, with four known outcomes as of January 2021, including three healthy newborns (including one preterm), and one spontaneous miscarriage at 13 weeks in a 36-year-old mother (early first trimester exposure to BAR with concomitant medications for RA including HCQ, GOL, prednisolone, MTX, folic acid and ibuprofen) [402].

UKTIS does not reported on JAKi. We found no evidence relating to breastmilk exposure to JAKi. Given that they are small molecules and likely to transfer into breastmilk, they should be avoided. LactMed states that no information is available on the use of TOF or BAR during breastmilk exposure, and alternate drugs are preferred, especially while nursing a newborn or preterm infant [192].

There were no studies identified that met our inclusion criteria for UPA. Data provided by AbbVie included 54 maternal pregnancies inadvertently exposed to UPA in the month prior to conception or during the first trimester of pregnancy during the clinical trials programme [403]. The 41 known outcomes included 17 healthy live births (including two premature deliveries), 14 spontaneous miscarriages (10 of whom were on concomitant MTX), nine elective terminations (all with no reported foetal defects) and one ectopic pregnancy. Filgotinib was NICE-approved after our search window, and so was not included in our search.

Recommendations for JAK inhibitors in pregnancy and breastmilk exposure

i) There are insufficient data to make a recommendation on JAKi use during pregnancy and they should be stopped at least two weeks before planned conception (GRADE 2C, SOA 99.5%).
ii) There are insufficient data to recommend JAKi in breastfeeding and, given they are likely to transfer into breastmilk, they should be avoided (GRADE 2C, SOA 99.5%).

Paternal exposure

Hydroxychloroquine

For HCQ, no additional paternal exposures were identified to the previously identified cohort study [52] and case series [404] of 13 pregnancies after paternal exposure to HCQ, which did not find any increased risk of adverse foetal outcomes.

Corticosteroids

Previously, four cohort studies [52, 405–407] and two case series [404, 408] reported on outcomes from ≥2127 pregnancies after paternal exposure to prednisolone, and a case-control study [409] and a case series [410] reported on outcomes from ($n = 4$) pregnancies after paternal exposure to methylprednisolone. Overall, the quality of these studies was low, but reassuringly they did not identify an increased risk of adverse foetal outcomes. Since then, an additional study of 2380 paternal exposures to corticosteroids did not identify any statistically significant increase in adverse birth outcomes [411].

Methotrexate

Previous low-quality evidence from outcomes of pregnancies after paternal exposure ($n = 263$) to predominantly low-dose MTX did not find any adverse effects [1]. We identified an additional six studies of paternal exposures to MTX ($n = 2026$) within three months of conception that similarly found no increased risk of adverse foetal outcomes when compared with MTX-unexposed controls ($n = 4\,700\,599$) [184–189]. An additional study examined foetal outcomes with paternal MTX (and other DMARD) use compared with abatacept; however, outcomes for individual drugs were not reported [375].

Sulfasalazine

Our previous review of three cohort [52, 407, 412] and one case-control study [409] reporting on 237 pregnancies after paternal exposure to SSZ did not find an increased risk of adverse foetal outcomes, although the quality of evidence was low. SSZ may also affect male fertility, with oligospermia, reduced sperm motility and increased proportions of abnormal sperm previously reported [1]. No further studies of paternal SSZ exposure were identified in our search.

Leflunomide

Previously, we identified a cohort study [52] and case report [413] describing outcomes from ($n = 2$) pregnancies after paternal exposure to LEF within three months of conception, and subsequent pregnancy exposure (with intercourse without a condom) in at least one case with no reported washout. No adverse foetal outcomes were observed. An additional study was identified examining foetal outcomes with paternal leflunomide (and other DMARD) use compared with abatacept; however, outcomes for individual drugs were not reported [375].

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Azathioprine

In addition to the previous 602 paternal exposures [52, 404–409, 414, 415], we identified three studies of $n = 2680$ pregnancies after paternal exposure to AZA [185, 187, 216]. Overall, no increased risk of adverse foetal outcomes was observed.

Ciclosporin

In addition to previous studies [406, 408, 410, 416] on outcomes from pregnancies ($n \geq 254$) after paternal exposure to CsA, we found a Danish population-based cohort study of birth outcomes in 247 children fathered by men treated with CsA before conception [185]. Overall, these studies did not identify an increased risk of adverse foetal outcomes with paternal exposure to CsA.

Tacrolimus

No additional paternal studies were found to complement previous findings reporting outcomes from pregnancies ($n \geq 120$) after paternal exposure to tacrolimus, which did not identify an increased risk of adverse foetal outcomes [406, 416, 417].

Cyclophosphamide

No new studies of paternal exposure to CYC were identified. In addition to a potential long-term impact on spermatogenesis (and hence fertility) in men [418], there is evidence of an adverse impact on germ cell development and male-mediated teratogenicity from animal studies [419–422], although this has not been proven in humans [423–425].

Mycophenolate mofetil

In addition to the three previous studies [406, 416, 426] of paternal exposures to MMF ($n \geq 72$), we found three additional studies of pregnancies ($n = 220$) after paternal exposure [185, 246, 247]. Overall, the quality of these studies was low, but they did not identify an increased risk of adverse foetal outcomes.

Intravenous immunoglobulin

There is no evidence relating to paternal exposure but based on maternal compatibility it is unlikely to be harmful.

Anti-TNFα drugs

Previously, we found five cohort studies [52, 263, 405, 412, 427], two case series [404, 410], two case reports [428, 429] and a case-control study [409] that reported on outcomes from pregnancies ($n = 131$) after paternal exposure to INF, ETA and ADA. Overall, the quality of these studies was deemed to be low, but they did not identify an increased risk of adverse foetal outcomes. We identified an additional eight cohort studies reporting outcomes from 620 pregnancies after paternal exposure to TNFi [293, 298, 306, 430–434], with no significant findings to suggest adverse foetal outcomes were more likely after TNFi exposure.

Rituximab

We did not identify any further paternal exposures to the 11 found previously [343], which did not identify any problems in relation to paternal exposure to RTX.

IL-6 Inhibitors

Two studies of $n = 15$ paternal exposures to TCZ did not find any drug-related effects [357, 359].

IL-1 Inhibitors

One study of $n = 5$ paternal exposures to anakinra did not find any drug-related effects [369]. Youngstein *et al.* reported on five healthy pregnancies to three fathers on long-term canakinumab treatment [369].

Abatacept

In addition to the previous case of one healthy pregnancy following paternal ABA exposure [374], a study of clinical trial and post-marketing data submitted to the manufacturer (up to 2014) reported 10 paternal ABA exposures, resulting in nine healthy live births with one elective termination [375].

IL-17 inhibitors

Two studies of paternal exposure to secukinumab ($n = 54$) and ixekizumab ($n = 34$) did not report any adverse drug-related effects [387, 389].

JAK-inhibitors

There were 87 paternal exposures to TOF in a study included in our search [397]. Further details provided by Pfizer reported paternal exposures to TOF in the PsA clinical trials ($n = 3$) and post-marketing reports ($n = 3$), described above. During the RA and psoriasis clinical trials programmes, 66 men were exposed to TOF with 45 known outcomes, including 37 normal healthy newborns, two premature deliveries (with one subsequent neonatal death) and six spontaneous miscarriages [400]. In the UC clinical trial programmes, there were 19 paternal exposures with 17 known outcomes (15 healthy newborns including one healthy preterm delivery at 34 weeks, and two spontaneous miscarriages) [398]. Data provided by Eli Lilly included eight paternal exposures to BAR in the clinical trials programmes, and outcomes included six full-term healthy newborns and two spontaneous miscarriages [402].

No data were found relating to paternal exposure to BEL, IL-12/23i or anifrolumab.

Recommendations for paternal exposure to immunomodulatory drugs

i) Due to the adverse effect of CYC on male fertility, semen cryopreservation is recommended for men prior to paternal exposure (GRADE 1C, SOA 99.5%).
ii) Men who take SSZ may have reduced fertility. There is little evidence to suggest that SSZ should be stopped preconception, unless conception is delayed by more than 12 months when stopping SSZ should be considered along with other causes of infertility (GRADE 1C, SOA 99.0%).
iii) Paternal exposure to the following anti-rheumatic medication is compatible with pregnancy: prednisolone, low-dose (≤25 mg/week) MTX, AZA (GRADE 1B); TNFi, cyclosporin (GRADE 1C); HCQ, LEF, tacrolimus, MMF, IVIG, RTX, IL-6i, IL-1i, ABA, BEL, IL-17i, UST and JAKi (GRADE 2C, SOA 99.3%).

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Applicability and utility

Implementation

Awareness of these guidelines will aid clinical practitioners and patients in decision making and will be raised through presentation at local, regional and national meetings. No barriers to implementation of these guidelines are anticipated.

Key standards of care

Ideally, patients with rheumatic disease should receive tailored pre-pregnancy counselling and then be reviewed during pregnancy and the four-month post-partum period by clinical practitioners with expertise in the management of rheumatic disease in pregnancy, in addition to their routine obstetric care. They should have access to written information on relevant medications in pregnancy and breastfeeding that is accurate and allows them to make informed decisions regarding compatibility of certain drugs in pregnancy.

Future research agenda

The limitation of current evidence highlights the need for a national pregnancy registry for patients with rheumatic disease, as currently exists for women with epilepsy. All women with rheumatic disease who become pregnant would be eligible to register, whether or not they are on anti-rheumatic treatment. The prospective pregnancy outcome data would then be published to display information on outcomes such as miscarriage and congenital anomalies in patients treated with anti-rheumatic therapy. These data would also be used to answer specific questions such as the most suitable time to stop MTX pre-conception. Data relating to the impact of paternal exposure to these drugs (both fertility and male-mediated teratogenicity), as well as breastmilk exposure, are particularly limited, and further research in these areas is urgently required. Other research questions include: should bDMARDs with known placental transfer be stopped or switched before/during pregnancy; are tsDMARDs compatible with pregnancy; is it safe to give certain live vaccines to infants $\leq$6 months after *in-utero* exposure to bDMARDs with known placental transfer in the third trimester of pregnancy?

Mechanism for audit of the guideline

An audit pro forma to assess compliance with these guidelines is shown in the audit tool in Supplementary Data S5, available at *Rheumatology* online.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability statement

All relevant data produced during the guideline development process are presented in the guideline or in the accompanying supplementary material.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: All authors have made declarations of interest in line with BSR policy (see Supplementary Material, available at *Rheumatology* online). L.M. has received honoraria from UCB and educational funding support from Abbvie and Pfizer. C.G. has received honoraria from Abbvie, Alumis, Amgen, Astra-Zeneca, MGP, Sanofi and UCB. C.-S.Y. has received honoraria from Amgen. K.Sc. has received educational support from UCB and honoraria from UCB and Thermo-Fisherworks and a Novo Nordic Foundation research grant. L.W. has received honorarium from Novartis. M.R. has received educational funding support from Lilly, Pfizer, Janssen and UCB and honoraria from Lilly, Menarini and Biogen. S.T. has received honoraria from UCB. I.G. has received honoraria and unrestricted research grants from UCB. K.H. has received honoraria and educational support from UCB. M.G. has received honoraria from UCB, Lily and Abbvie. M.K. is an employee of GSK and gave independent expert advice to the Working Group. The remaining authors have declared no conflicts of interest.

Acknowledgements

A full list of Standards, Audit and Guidelines Working Group members can be found in Supplementary Data S6, available at *Rheumatology* online. All contributing members are named in the authorship list.

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Rheumatology, 2022, **00**, 1–16
https://doi.org/10.1093/rheumatology/keac552
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Guidelines

British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: comorbidity medications used in rheumatology practice

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Keywords: rheumatic disease, pregnancy, breastfeeding, prescribing, analgesics, NSAIDs, anticoagulants, antihypertensive drugs

Received: 9 September 2022. **Accepted:** 14 September 2022
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Scope and purpose

Background

The rationale behind this update on the 2016 British Society for Rheumatology (BSR) guidelines on prescribing antirheumatic drugs in pregnancy and breastfeeding [1, 2] was described in detail in the guideline scope [3]. In brief, despite the existence of additional evidence-based guidelines on prescribing/managing rheumatic disease in pregnancy [4–7] the information contained within them requires continual review to include emerging information on the safety of new and existing drugs in pregnancy.

Chronic disease adversely affects pregnancy. Data from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK), reports regularly from a national programme of work conducting surveillance and investigating the causes of maternal deaths, stillbirths and infant deaths [8]. Data from 2017–19 found that 8.8 women per 100 000 died during pregnancy or up to six weeks after childbirth or the end of pregnancy, and most women who died had multiple health problems or other vulnerabilities [8]. In all decisions regarding medication choices and changes, it is also important to consider the potential for deterioration in the mother's wellbeing through side effects or reduced disease control (and its adverse impact on the baby). Therefore, the exposure of the foetus to different drugs when switches are made must be balanced against possible foetal gains and understanding the potential impact of reduced control of the medical disorder on a pregnancy is vital [9].

Need for guideline

Patients with inflammatory rheumatic disease (IRD) should be counselled to achieve and then maintain remission or low disease activity before/during pregnancy to reduce the risk of adverse pregnancy outcomes [10]. This goal is primarily achieved through adjustment of therapy to ensure disease control with disease modifying anti-rheumatic drugs (DMARDs) and/or immunosuppressive drugs that are compatible with pregnancy. These medications are reviewed in the BSR guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids [11]. Many patients with IRD, however, have an additional burden of pain and comorbid illness [12] that require treatment with other medications. The compatibility of various comorbidity medications relevant to rheumatic disease will be covered in this update. This updated information will provide advice for healthcare professionals and patients to ensure more confident prescribing in these scenarios and will highlight any medications that should be stopped and/or avoided in the reproductive age group unless highly effective contraception is used, in line with guidance issued by the Medicines and Healthcare Products Regulatory Agency (MHRA) and Faculty of Sexual and Reproductive Healthcare [13, 14].

Objectives of guideline

To update the previous BSR guidelines on prescribing in pregnancy in rheumatic disease for the following drug categories: pain management; NSAIDs and low-dose aspirin (LDA); anticoagulants; colchicine; dapsone; bisphosphonates; anti-hypertensives; and pulmonary vasodilators. This revised guideline was produced by consensus review of current evidence to answer specific questions in relation to each drug as follows. Should it be stopped pre-conception? Is it compatible with pregnancy? Is it compatible with breastmilk exposure? Where possible, recommendations are made regarding compatibility with paternal exposure.

Target audience

The primary audience consists of health professionals in the UK directly involved in managing patients with rheumatic disease who are (or are planning to become) pregnant and/or breastfeeding, men planning to conceive, and patients who have unintentionally conceived while taking these medications. This audience includes rheumatologists, rheumatology nurses/allied health professionals, rheumatology speciality trainees and pharmacists, as well as the patients themselves. The guideline will also be useful to obstetricians, obstetric physicians, renal physicians, dermatologists and general practitioners who may prescribe these medications to patients in pregnancy.

This guideline uses the terms 'woman', 'maternal' or 'mother' throughout. These should be taken to include people who do not identify as women but are pregnant or have given birth [15]. Where the term 'breastfeeding' is used in this guideline it also refers to infant breastmilk exposure via other methods (e.g. expressed breastmilk, administered via a bottle).

The areas the guideline does not cover

This guideline does not cover the management of infertility or acute pain relief during labour, hence morphine was excluded. Other drug categories: antimalarials; corticosteroids; disease modifying anti-rheumatic and immunosuppressive therapies; and biologic drugs are considered in another guideline [11]. All recommendations in this guideline were formulated by the working group on the basis of published evidence at the time of the systematic literature search, and do not necessarily refer to licensing information or Summary of Product Characteristics for individual medications.

Stakeholder involvement

This guideline was commissioned by the BSR Standards, Audit and Guidelines Working Group. A Guideline Working group (GWG) was created, consisting of a chair (I.G.), alongside representatives from relevant stakeholders (Table 1). In accordance with BSR policy, all members of the GWG made declarations of interest, available on the BSR website.

Involvement and affiliations of stakeholder groups involved in guideline development

The GWG consisted of rheumatologists from a range of clinical backgrounds, various allied health professionals, other specialists in women's health, lay members and representatives from the United Kingdom Tetralogy Information Service (UKTIS). All members of the working group contributed to the process for agreeing key questions, guideline content, recommendations and strength of agreement.

Rigour of development

Statement of scope of literature search and strategy employed

Most medications covered in this guideline have been comprehensively and systematically reviewed in multiple other documents, since the first BSR guideline on this topic. Therefore, a

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Table 1. Composition of Guideline Working Group: list of group members and relevant stakeholders

Tasks	Role	PICO definition	Data search	Data extraction	Voting member	Non-voting member	Manuscript authors
Karen Schreiber	Lead author, trainee rheumatologist	x	x	x	x		x
Margreta Frishman	Lead author, trainee obstetrician	x	x	x	x		x
Mark Russell	Trainee rheumatologist	x			x		
Mrinalini Dey	Trainee rheumatologist	x			x		
Julia Flint	Trainee rheumatologist	x			x		
Alexander Allen	Data analyst	x	x			x	
Amy Crossley	Patient representative					x	
Mary Gayed	Consultant rheumatologist	x			x		
Kenneth Hodson	Head of UK Tetralogy Information Service & consultant obstetrician	x			x		
Munther Khamashta	Consultant rheumatologist	x			x		
Louise Moore	Clinical nurse specialist	x			x		
Sonia Panchal	Consultant rheumatologist	x			x		
Madeleine Piper	Consultant rheumatologist	x			x		
Clare Reid	Patient representative	x				x	
Katherine Saxby	Pharmacist	x			x		
Naz Senvar	Trainee obstetrician	x			x		
Sofia Tosounidou	Consultant rheumatologist	x			x		
Maud van de Venne	Consultant obstetrician	x			x		
Louise Warburton	General practitioner	x			x		
David Williams	Consultant obstetric physician	x			x		
Chee-Seng Yee	Consultant rheumatologist	x			x		
Caroline Gordon	Consultant rheumatologist	x			x		
Ian Giles	Chair of working group & consultant rheumatologist	x	x	x	x		x

All members were involved in data review, formulation of recommendations and editing of the manuscript.

consensus-based approach was taken to compile and assess most significant evidence published since 2013 to December 2020 through a comprehensive search of MEDLINE, PubMed and EMBASE databases with specific search terms (Supplementary Table S1, available at *Rheumatology* online). Filters were applied to capture National Institute for Health and Care Excellence (NICE) guidance, international guidelines, systematic reviews, cohort studies or case series. Information was preferentially selected from NICE guidance and/or largest/most recent systematic reviews and where lacking was extracted from largest cohort, case series or abstract. Findings were cross-referenced with the previous BSR guideline [2], as well as the Cochrane, Lactmed (a National Library of Medicine database on drugs and lactation) and UKTIS databases.

Two independent reviewers screened the title and abstract of 2997 articles, identified 130 and selected the most recent/largest systematic reviews or largest cohort study or case series as well as any NICE guidance and international guidelines. Thirty-six studies (Fig. 1) met the inclusion criteria and relevant information was extracted into data-extraction tables.

Statement of methods used to formulate the recommendations (levels of evidence)

The working group met regularly to formalise search strategy, review evidence, resolve disagreements and finally to determine recommendations. This guideline was developed in line with BSR's Guidelines Protocol using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology to determine quality of evidence and strength of recommendation. Accompanying each recommendation in this guideline, in brackets, is the strength of recommendation, quality of evidence and strength of agreement (SOA).

Strength of recommendation

Using GRADE, recommendations were categorized as either strong (denoted by 1) or weak (denoted by 2), according to the balance between benefits and risks. A strong recommendation was made when the benefits clearly outweigh the risks (or vice versa). A weak recommendation denotes that the benefits are more closely balanced with the risk, or more uncertain.

Quality of evidence

Using the GRADE approach, the quality of evidence was determined as either high (A), moderate (B) or low/very low (C) reflecting the confidence in the estimates of benefits or harm.

Strength of agreement

The wording of each recommendation was discussed until all members were satisfied they would score at least 80 on a scale of 1 (no agreement) to 100 (complete agreement) and then 20/23 members with full voting rights scored each recommendation on the same scale and the average was calculated to generate a strength of agreement (SOA) score. Two patient representatives and a data-analyst expressed concern that they did not have sufficient medical knowledge of all drugs reviewed to score all recommendations, so while they fully agreed with each, they did not wish to score each one and did not contribute to the final SOA score.

Statement of any limits of search and when guideline will be updated

The search was conducted in December 2020. Limits were placed for English language and filters as described above. The guideline will be updated in five years.

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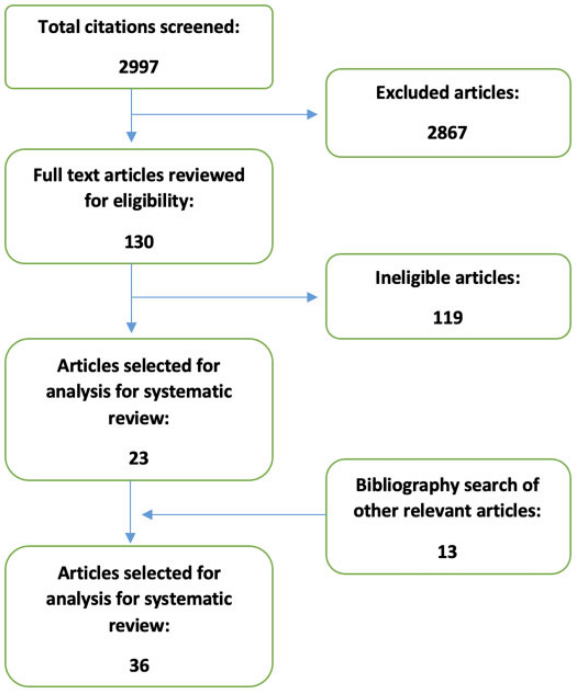

Figure 1. Flow diagram of study selection

The guideline

Drugs are considered in the following categories: pain management; NSAIDs and LDA in the management of multisystem rheumatic disease; anticoagulants; bisphosphonates; antihypertensive medication in the management of multisystem rheumatic disease; and pulmonary vasodilators. The overall findings for maternal and foetal breastmilk exposures to each drug, including information and key references from the previous BSR guideline [2] are summarised and recommendations updated accordingly. Paternal exposures and recommendations are described separately after maternal data. An overall summary of compatibility of each drug pre-conception, during pregnancy, breastmilk exposure and paternal exposure is shown in Table 2. Generic recommendations were developed based on evidence as shown in Supplementary Table S2, available at *Rheumatology* online.

Generic recommendations on prescribing in rheumatic disease in pregnancy

i) Pre-conception counselling should be addressed by all healthcare professionals, with referral to professionals with relevant experience as appropriate to optimize all therapy, including non-pharmacological options for chronic pain management during pregnancy (GRADE 1A, SOA 99.5).
ii) The risks and benefits of drug treatment to mother and foetus should be discussed and clearly documented by all healthcare professionals involved in the patient's care (GRADE 1A, SOA 99).
iii) The cause of pain and other symptoms should be assessed and managed appropriately (GRADE 1B, SOA 98.5).
iv) The requirement for analgesia should be assessed and minimum effective dose should be prescribed and titrated according to response (GRADE 1B, SOA 100).
v) Tricyclic antidepressants are preferred over other anti-depressant medications to manage chronic pain (GRADE 1B, SOA 98.1).
vi) Cessation of anti-depressant therapy that is being used as chronic pain medication in the post-natal period is not recommended, due to the risk of adverse impact on mood (GRADE 1C, SOA 96).
vii) LDA (≤150 mg/day) is recommended in all patients at high risk for pre-eclampsia (GRADE 1A, SOA 99.5).
viii) Low molecular weight heparin (LMWH) is the preferred anticoagulant (GRADE 1A, SOA 100).
ix) Nifedipine is the preferred vasodilator (GRADE 1B, SOA 98.5).
x) Paternal drug exposure may reduce male fertility but has not been associated with adverse foetal development or pregnancy outcome. Although evidence is weak, we recommend that men are reassured about the safety of fathering a pregnancy while taking medicines to manage comorbidities as described in this guideline (GRADE 1C, SOA 98).

Pain management: conventional analgesics

Paracetamol

Two systematic reviews [16, 17] were selected. Overall, paracetamol was considered to have a favourable safety profile in pregnancy. Potential links between paracetamol use in pregnancy and pre-term birth and adverse neurodevelopmental outcomes (principally autism and attention deficit hyperactivity disorder) were confounded by maternal disease and selection bias [16]. UKTIS states that 'In most studies, risk of abnormal neurodevelopment correlated with duration of paracetamol exposure. However, significant methodological limitations of these studies limit the conclusions that can be drawn, and a causal association remains unproven' [18].

There were no convincing associations with congenital malformations. UKTIS notes that findings of a possible increased risk of cryptorchidism in male offspring following paracetamol use during pregnancy are conflicting [18]. Current Royal College of Obstetricians (RCOG) guidance is that paracetamol remains safe for use during pregnancy and breastfeeding, and its use in any trimester does not appear to increase the risk of major birth defects [19].

There were conflicting results on the risk of developing wheeze in infants exposed to paracetamol during pregnancy. A recent meta-analysis of 13 articles and 1 043 109 individuals identified a statistically significant association between prenatal paracetamol exposure and increased risk of child asthma [odds ratio (OR) 1.19; 95% CI, 1.12, 1.27; $P < 0.00001$] in a random-effect model [17]. This significant association was observed for first trimester as well as second and third trimester exposure.

There were no studies identified which specifically examined neonatal outcomes after drug exposure in breastmilk. LactMed [20] reports low amounts of this drug in breastmilk at levels much less than doses usually given to infants with few reports of adverse events. The following recommendations for paracetamol were developed based on evidence as shown in Supplementary Table S3, available at *Rheumatology* online.

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Table 2. Summary of drug compatibility in pregnancy and breastfeeding

	Compatible peri-conception	Compatible with 1st trimester	Compatible with 2nd/3rd trimester	Compatible with breastfeeding	Compatible with paternal exposure
Conventional painkillers					
Paracetamol	Yes	Yes[a]	Yes[a]	Yes	Yes[b]
Codeine	Yes	Yes	Yes	Yes[a]	Yes[b]
Tramadol	No	No	Yes[a]	Yes[c]	Yes[b]
Other chronic pain treatments					
Amitriptyline	Yes	Yes	Yes	Yes	Yes[b]
Gabapentin	Yes	Yes[d]	Yes[d]	Yes	Yes[b]
Pregabalin	Yes	Yes[d]	Yes[d]	Yes	Yes[b]
Venlafaxine	Yes	Yes	Yes	Yes[e]	Yes[b]
Fluoxetine	Yes	Yes	Yes	Yes[c,e]	Yes[b]
Paroxetine	Yes	Yes	Yes	Yes[c,e]	Yes[b]
Sertraline	Yes	Yes	Yes	Yes[c,e]	Yes[b]
Duloxetine	Yes	Yes	Yes	Yes[e]	Yes[b]
NSAIDS					
NSAIDs	Yes	Yes[a,f]	Stop by week 30	Yes	Yes
COX-2 inhibitors	No	No	No	No	Yes[b]
Other drugs					
Colchicine	Yes	Yes	Yes	Yes	Yes[b]
Dapsone	Yes	Yes	Yes	Yes	Yes[b]
Anti-platelet agents					
LDA	Yes	Yes	Yes	Yes	Yes[b]
Clopidogrel	Yes[c]	Yes[c]	Yes[c]	Yes[c]	Yes[b]
Anticoagulants					
Warfarin	No	No	Exceptional circumstances only	Yes	Yes[b]
LMWH	Yes	Yes	Yes	Yes	Yes[b]
DOACs	No	No	No	Rivaroxaban only	Yes[b]
Fondaparinux	Yes[c]	Yes	Yes	Yes	Yes[b]
Bisphosphonates					
Bisphosphonates	Stop 3 months in advance	No	No	No data	Yes[b]
Antihypertensives					
ACEi/ARBs	Stop when pregnancy confirmed		Exceptional circumstances only	Yes (enalapril)[c]	Yes[b]
Nifedipine	Yes	Yes <90 mg/day	Yes <90 mg/day	Yes	Yes[b]
Amlodipine	Yes[c]	Yes[c]	Yes[c]	Yes[c]	Yes[b]
Labetalol*	Yes	Yes	Yes	Yes	Yes[b]
Methyldopa*	Yes	Yes	Yes	Yes	Yes[b]
Pulmonary vasodilators					
Sildenafil		Multi-disciplinary team assessment		No data	Yes[b]
Bosentan		Multi-disciplinary team assessment		No data	Yes[b]
Prostacyclines		Multi-disciplinary team assessment		No data	Yes[b]

For further information and caveats, see relevant recommendations and main text in Executive Summary and full Guideline.
[a] Intermittent use advised – see main text for details.
[b] Based on limited data and no association with adverse foetal development or pregnancy outcome; therefore, unlikely to be harmful.
[c] Limited evidence, but unlikely to be harmful.
[d] Limited evidence regarding use for treatment of chronic pain in pregnancy. High-dose folic acid (5 mg/day) recommended.
[e] Cessation of anti-depressant therapy in post-natal period is not recommended.
[f] Possible association with miscarriage and malformation.
* Drugs not included in original search, but added due to relevance.

Recommendations for paracetamol in pregnancy and breastfeeding

i) Paracetamol is the analgesic of choice and compatible peri-conception and throughout pregnancy (GRADE 1B, SOA 99).
ii) LactMed describes paracetamol as a good choice for analgesia and fever reduction in breastfeeding mothers (GRADE 2C, SOA 99.5).

Codeine

One systematic review [16] considered outcomes from opioid-exposed pregnancies, including three studies of congenital malformation in >20 000 codeine-exposed pregnancies with conflicting results. Of these three studies, a large Norwegian population-based cohort study [21] found no statistically significant associations between neonatal codeine exposure and congenital malformations. In contrast, a large case-control study found that first trimester exposure to opioids (codeine and hydrocodone in 69% of cases) was significantly associated with congenital heart defects, spina bifida and gastroschisis [22], although there was a high risk for recall bias in this study. A case-control study found a significant association between spina bifida in infants and first trimester maternal opioid use, although it was not with codeine use

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specifically and potential confounders such as illicit drug use/dependence and sociodemographic data exist in this study [23]. UKTIS notes that the methodological limitations of studies make it difficult to draw any firm conclusions and more robust research is needed before firm conclusions regarding the risk of congenital anomalies with codeine use can be provided [18].

No convincing associations between first trimester opioid use and miscarriage have been found. A large population study found increased rates of premature delivery, reduced birthweight and pre-eclampsia in codeine-exposed patients compared with controls that was considered to be due to confounding factors such as maternal disease and lack of adjustment for gestational age [21]. This study also found a significant increase in post-partum haemorrhage (18.3% *vs* 14.5%; OR 1.3; 95% CI 1.1, 1.5) in 2666 mothers exposed to codeine [21] and hypothesized it was due to an opioid effect weakening myometrial contraction, but the precise mechanism is unknown.

UKTIS describes theoretical concerns that maternal use of codeine near term may be associated with respiratory depression in the neonate and notes that the only study that has investigated the risk of neonatal respiratory depression found no increased risk [18]. The potential risk of neonatal abstinence syndrome (NAS) is lower with short courses of short-acting opioids and must be weighed against the benefits for treating acute pain that often outweigh risks. Prolonged opioid use, however, should be avoided and if used in the last trimester, neonatologists should be advised due to the risks of NAS [16].

Controversy remains over whether codeine is safe in breastfeeding. Central nervous system (CNS) depression was reported by mothers in 16.7% (35/210) babies exposed to codeine, compared with 0.5% exposed to paracetamol [24]. In the same study there was one neonatal death and high morphine levels were found at post-mortem. The mother had received high doses of codeine (>2 mg/kg/day) and was subsequently found to be an ultra-rapid CYP2D6 metaboliser. Another study demonstrated dose-dependent CNS depression in 24% (17/72) of infants exposed to codeine through breastmilk [25]. A large study of 7804 infants reported conflicting results, but specifically, there was no difference in poor Apgar scores, postnatal complications, admission to special care baby units, readmission to hospital, resuscitation or death in infants exposed and not exposed to codeine [26].

LactMed notes that numerous professional organizations and regulatory agencies recommend that other agents are preferred over codeine during breastfeeding but that other opioid alternatives have been less studied and may not be safer [20]. It is acknowledged that due to its unpredictable metabolism, administration of codeine results in delivery of an unknown quantity of morphine. Therefore, despite its widespread use and probable safety in most cases, we would advise caution with prolonged use of codeine in breastfeeding and appropriate advice to the mother to seek medical attention if she has any concerns regarding lethargy or drowsiness in her child. The following recommendations for codeine were based on evidence as shown in Supplementary Table S3, available at *Rheumatology* online.

Recommendations for codeine in pregnancy and breastfeeding

i) Codeine is compatible peri-conception and throughout pregnancy, although long-term use should be avoided. There is no consistent evidence to recommend a dose reduction pre-delivery but neonatologists should be aware of maternal use (GRADE 1B, SOA 97.8).
ii) Caution is advised with use of codeine in breastfeeding, due to the risk of CNS depression resulting from unpredictable metabolism of codeine to morphine (GRADE 1C, SOA 98).

Tramadol

A systematic review [16] considered outcomes from tramadol-exposed pregnancies. It included a large prospective cohort study of over 1.6 million women [27] that reported a statistically significant association between tramadol use in pregnancy and major congenital malformations (OR 1.33; 95% CI 1.05, 1.70) and cardiovascular defects (OR 1.56; 95% CI 1.04, 2.29), although it did not adjust for indication, duration or dose of medication.

UKTIS notes that a single study identified an increased risk of miscarriage among women who used tramadol in early pregnancy and recommended further studies considering the impact of confounding factors to clarify this finding. A single cohort study found no increased risk of preterm delivery within 146 pregnancies exposed to tramadol in at least the first trimester [18]. A small number of case reports have reported NAS with long-term intrauterine exposure to tramadol [28], although none have compared the relative rate of NAS with tramadol compared with other opioid analgesics.

LactMed states that the excretion of tramadol into milk is low and even lower amounts of the active metabolite, O-desmethyltramadol, are excreted and a study of breastfeeding in newborn infants found no adverse effects attributable to tramadol compared with controls [20]. There has been one death, however, in the 8-month-old breastfed infant of a woman addicted to tramadol, although the death was not definitely attributable to tramadol exposure in breastmilk [29]. Current RCOG advice states that tramadol can continue to be used (with caution) during breastfeeding and the lowest effective dose should be used for the shortest time possible [19]. The following recommendations for tramadol were based on evidence as shown in Supplementary Table S3, available at *Rheumatology* online.

Recommendations for tramadol in pregnancy and breastfeeding

i) Avoid tramadol peri-conception and in first trimester and only consider in second/third trimester if no alternative analgesia (GRADE 2B, SOA 97.8).
ii) Based on limited data, tramadol may be compatible with short-term use in breastfeeding (GRADE 2C, SOA 94.8).

Other treatments for chronic pain

Amitriptyline

NICE guidance [30] and a systematic review [16] described amitriptyline use in pregnancy. Notably, the evidence base underlying amitriptyline use in pregnancy comes from its use as a tricyclic antidepressant (TCA) to treat depression at doses of 150–300 mg and evidence of its use in pregnancy to treat chronic widespread pain at 75 mg per day or less is lacking. In addition, most studies report on TCAs as a drug class and although they include (some) women exposed to amitriptyline, they lack a separate assessment of their pregnancy outcomes so do not provide information about specific amitriptyline exposure [18].

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Overall, no increased risk of congenital malformations has been found for TCAs [16]. UKTIS reports conflicting findings, with possible associations with spontaneous abortion, preterm delivery, and autism spectrum disorder identified in some (but not all) studies [18]. There is an association between discontinuation of antidepressants and a high risk for relapse of mood disorders that can adversely impact on pregnancy. It is unknown, however, whether a similar phenomenon of rebound pain exists when antidepressants used for analgesia are discontinued in pregnancy, particularly for amitriptyline that is used at 2–4-fold higher doses to treat depression compared with chronic pain. If a decision is made to stop amitriptyline in pregnancy, the dose should be tapered gradually where possible [16, 30].

Low levels of amitriptyline and its metabolites are reported in breastmilk with no adverse effects described with limited follow-up, summarised in LactMed [20]. The following recommendations were based on evidence as shown in Supplementary Table S4, available at *Rheumatology* online.

Recommendations for amitriptyline in pregnancy and breastfeeding

i) Amitriptyline is compatible with pregnancy. There is no evidence of adverse effect on IQ or developmental outcomes (GRADE 1C, SOA 100).
ii) Because very little amitriptyline is found in breastmilk with antidepressant doses and it is used at lower doses for chronic pain, it is unlikely to cause adverse effects in breastfed infants (GRADE 1C, SOA 100).

Gabapentin and pregabalin

Data on gabapentin use in pregnancy comes mostly from studies of the treatment of maternal epilepsy at doses generally higher that those used to treat chronic pain, while information on pregabalin use in pregnancy comes from studies of its use to treat neuropathic pain [18]. A systematic review [16] of gabapentin use in pregnancy to treat epilepsy did not find any evidence of an increased rate of major malformations or other adverse outcomes attributable to gabapentin exposure. No long-term outcomes were reported. Furthermore, a systematic review and meta-analysis published in abstract form only [31], of eight cohort studies (four prospective and four retrospective), reporting 5 072 286 unexposed and 949 exposed pregnancies found that first trimester exposure to gabapentin was not statistically significantly associated with major congenital malformations (OR 0.83; 95% CI 0.45, 1.53).

A prospective cohort study using Teratology Information Services data from seven European countries [32] found that first trimester use of pregabalin was associated with significantly higher rates of major congenital malformations when compared with unexposed pregnancies (OR 3.0; 95% CI 1.2, 7.9). This study, however, was limited by a small sample size (164 exposed pregnancies) and lack of adjustment for potential confounding by use of concomitant medications [16]. A systematic review of pregabalin use, mostly to treat neuropathic pain in pregnancy, including data from this study and two others identified 651 pregnancy exposures and concluded that pregabalin exposure during pregnancy is not devoid of structural teratogenicity potential [33]. UKTIS reviewed data from six controlled studies, with outcomes of >3000 exposed pregnancies of patients with chronic pain or other non-epilepsy indications. They conclude that this data does not indicate that maternal pregabalin use in pregnancy is associated with increased risks of malformation, miscarriage or adversely affects foetal growth [18]. Interestingly, a systematic review and meta-analysis published in abstract form only [34], of six studies reporting 2319 exposed pregnancies and 4 982 778 unexposed pregnancies found that first trimester exposure to pregabalin was not significantly associated with an increased risk of major congenital malformations (OR 1.20; 95% CI 0.92, 1.57).

Following completion of our guidelines, the MHRA issued a safety warning on the use of pregabalin in pregnancy based on new data available online [35]. This new data has been considered in the latest UKTIS update in April 2022 that states that the available data do not provide conclusive evidence that maternal pregabalin use in the first trimester, or at any stage of pregnancy, is associated with increased risks of either overall malformation or any specific malformations. Therefore, our recommendations have not changed.

UKTIS found no controlled studies of the risk of neonatal complication following prenatal gabapentin or pregabalin exposure, although one study has described a small number of affected infants, including one case of neonatal withdrawal following *in-utero* pregabalin exposure [18]. Use of any centrally acting drug throughout pregnancy or near delivery may be associated with withdrawal symptoms in the neonate and/or NAS.

Although evidence is lacking and it is uncertain if pregabalin or gabapentin impact upon maternal folate status, UK guidelines state that women who take any anti-epileptic medication should be prescribed high-dose folic acid (5 mg/day) preconceptually and in the first trimester [19].

There remains limited data on use of these drugs in breastfeeding. According to LactMed, low levels of gabapentin and pregabalin have been found in breastmilk with no adverse effects on infants reported in limited case reports/series ($n < 10$) for gabapentin. Therefore, both drugs may be considered if required by the breastfeeding mother [20]. The following recommendations were based on evidence as shown in Supplementary Table S4, available at *Rheumatology* online.

Recommendations for gabapentin and pregabalin in pregnancy and breastfeeding

i) Gabapentin at lowest effective dose may be considered in pregnancy with folic acid supplementation if no alternative analgesic is suitable (GRADE 1B, SOA 95).
ii) Gabapentin may be considered in breastfeeding if no alternative analgesic is suitable (GRADE 2C, SOA 96).
iii) Pregabalin may be considered in pregnancy (with folic acid supplementation) and during breastfeeding (GRADE 2C, SOA 95.3).

Serotonin–norepinephrine reuptake inhibitors (SNRIs)

NICE guidance [30] and two systematic reviews [16, 33] described SNRI use in pregnancy. There was no association between first trimester exposure to venlafaxine and an increased risk for major congenital malformations [16]. UKTIS notes that although there are some reports of an increased risk of miscarriage following gestational exposure to venlafaxine, the data are inconsistent and likely confounded by indication and other factors [18]. Some studies have found a possible association with an increased risk for some perinatal complications, including a withdrawal syndrome with venlafaxine use in the

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third trimester [16]. A more limited data set for duloxetine does not suggest a clinically important increased risk for major malformations but has identified prenatal antidepressant exposure syndrome in two of five case reports and conflicting reports of increased rates of gestational hypertension and spontaneous abortion [33].

LactMed reports that infants receive venlafaxine and its active metabolite in breastmilk, and the metabolite of the drug can be found in the plasma of most breastfed infants, but no proven drug-related side effects have been reported in small case series. Little published information is available on the use of duloxetine during breastfeeding; however, the dose in milk is low and serum levels were low in two breastfed infants [20]. The following recommendations were based on evidence as shown in Supplementary Table S4, available at *Rheumatology* online.

Recommendations for SNRIs in pregnancy and breastfeeding

i) Venlafaxine is compatible at conception and throughout pregnancy. There may be an increased risk of neonatal abstinence syndrome/short-term behavioural effects, but larger studies are needed to evaluate this finding (GRADE 2C, SOA 95.8).
ii) Duloxetine may be considered in pregnancy and breastfeeding but there are fewer data than for venlafaxine (GRADE 2C, SOA 95.3).
iii) Venlafaxine and duloxetine may be considered in breastfeeding if there is no alternative chronic pain medication (GRADE 2C, SOA 95.8).

Selective serotonin reuptake inhibitors (SSRIs)

NICE guidance [30] and a systematic review [16] described SSRI use to treat depression in pregnancy. The SSRIs are used to treat chronic pain at similar doses used to treat depression. A systematic review considered data from >50 000 infants exposed to SSRIs *in utero*, which did not show an overall increased risk for congenital malformations [16]. It describes ongoing debate about the risk for cardiovascular malformations with first-trimester use of SSRIs with risk found from some [36, 37] but not all studies [38, 39]. Overall, any increase in absolute risk was thought unlikely to be clinically significant and may be associated with particular SSRIs, principally fluoxetine and paroxetine [36, 37].

The UKTIS summary of findings to date from studies on SSRIs states that a causal association between use of SSRIs in pregnancy and any type of congenital malformation has not been confirmed. It also describes conflicting results from other outcomes and concludes that available data do not suggest that SSRI use in pregnancy increases the risk of stillbirth and that possible associations with neurodevelopmental impairment in infants requires further study. An increased risk, however, of persistent pulmonary hypertension (PPHN) of the newborn has also been reported following exposure to SSRIs as a class beyond 20 weeks of gestation and, although it remains an uncommon event (0.2–1.2% *vs* 0.1–0.2% in the background population), it represents a potentially serious neonatal complication [18]. Because there is no robust evidence of a superior safety profile for any one drug, switching between drugs is not recommended if depression is stable on treatment.

NICE recommendations on use of TCAs, SSRIs or SNRIs include consideration of: the uncertainty about whether any increased risk to the foetus and other problems for the woman or baby can be attributed directly to these drugs or may be caused by other factors; and the risk of discontinuation symptoms in the woman and neonatal adaptation syndrome in the baby with most TCAs, SSRIs and (S)NRIs, in particular paroxetine and venlafaxine [30].

There is limited information on the use of these drugs in breastfeeding. One small study showed temporarily reduced growth during exposure to fluoxetine in breastmilk. There have been no studies specifically investigating compatibility of paroxetine and sertraline with breastfeeding, but sertraline is reported as having one of the lowest rates of transmission to breastmilk [20]. The following recommendations were based on evidence as shown in Supplementary Table S4, available at *Rheumatology* online.

Recommendations for SSRIs in pregnancy and breastfeeding

i) Fluoxetine, paroxetine and sertraline are compatible with pregnancy (GRADE 1B, SOA 98.8).
ii) Based on limited evidence, SSRIs are compatible with breastfeeding (GRADE 2C, SOA 98.3).

NSAIDs and anti-platelet drugs

Non-selective cyclooxygenase (COX) inhibitors have different indications in pregnancy. NSAIDs have analgesic and anti-inflammatory actions mediated through peripheral inhibition and differential selectivity of COX enzymes. In contrast, LDA at doses ≤150 mg/day is used to prevent thrombosis and pre-eclampsia in high-risk groups throughout pregnancy in patients with rheumatic diseases. Clopidogrel is an anti-platelet agent that may sometimes be used with or instead of LDA to reduce cardiovascular risk. NICE guidance [40], four systematic reviews [16, 41–43] and a case report/review [44] evaluated LDA, NSAID and clopidogrel use in pregnancy.

NSAIDs and COX-2 inhibitors

Overall, there is no consistent evidence for an increased risk of teratogenic effects with NSAID use in pregnancy. There are mixed findings regarding a potential increased risk for miscarriage, with findings limited by methodology and larger associations reported for indomethacin and diclofenac use in the periconceptional period [16]. There was no information on safety of COX2 inhibitors in pregnancy. NSAIDs are reported to increase the incidence of luteinized unruptured follicle (LUF) syndrome, whereby an anovulatory cycle results due to failure of normal follicular wall rupture despite normal ovarian follicular development and elevation of serum progesterone. COX-2 is active in the ovaries during follicular development; thus, inhibition via COX-2 inhibitors is thought to result in LUF. Although similar findings have been reported for both COX-1 and COX-2 NSAIDs, the risks have been found to be greater in patients with inactive disease and in those taking a COX-2 inhibitor (etoricoxib) rather than non-selective NSAIDs and it is reversible, following drug withdrawal [16].

A systematic review of the effects of various drugs on foetal cardiac function evaluated by ultrasound found that all NSAIDs (including COX2 inhibitors) increased constriction in the ductus arteriosus, within 4–30 h of exposure and resolved by 72 h of discontinuation [43]. In this study the critical gestational age (measured for indomethacin)

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increased from 5–10% of foetuses at weeks 26–27 to 50% at week 32.

In 2020 the United States Food and Drug Administration (FDA) recommended that all NSAIDs be avoided from gestational week 20 rather than the previously advised 30 weeks. This advice was based on their updated review of published data to 2016 and 35 cases reported to FDA identifying an increased risk of oligohydramnios and renal impairment that began at 20 weeks of gestation and were mostly reversible on stopping NSAID. They clarify their advice for healthcare professionals, stating that the use of NSAIDs between 20 and 30 weeks of pregnancy should be limited to the lowest effective dose for the shortest duration [45].

Low-dose aspirin

LDA has been extensively studied and shown to improve outcomes in high-risk pregnancies. A Cochrane review of 77 trials, involving 40 249 women and their babies, found high quality evidence that antiplatelet agents (mostly LDA up to 150 mg/day) reduced pre-eclampsia and its complications [42]. A systematic review of 22 RCTS of LDA plus heparin compared with other treatments in patients with APS, including 1515 treatment and 1531 control subjects, found that adverse pregnancy outcomes were significantly improved with LDA and heparin [41]. The use of LDA in the third trimester of pregnancy is not associated with premature closure of ductus arteriosus and NICE guidelines for management of hypertension in pregnancy advises treatment with LDA until delivery [40].

Clopidogrel

There was no demonstrable maternofoetal toxicity in 13 (mostly second and third trimester only) pregnancy exposures to clopidogrel [44]. UKTIS does not report on clopidogrel.

LactMed considers various non-selective NSAIDs to be acceptable during breastfeeding and prefers ibuprofen because of its extremely low levels in breastmilk, short half-life and safe use in infants in doses much higher than those excreted in breastmilk, as an analgesic or anti-inflammatory agent in breastfeeding mothers. There was no information on COX2 inhibitors. Aspirin doses up to 325 mg daily are not excreted into breastmilk so LDA may be considered as an antiplatelet drug for use in breastfeeding women and is preferred to clopidogrel as no information is available on this drug [20]. Recommendations for these drugs were based on evidence as shown in Supplementary Tables S5 and S6, available at *Rheumatology* online.

Recommendations for NSAIDs and COX-2 inhibitors in pregnancy and breastfeeding

i) Discordant findings from retrospective, large studies with population controls on the use of non-selective NSAIDs in the first trimester of pregnancy raise the possibility of a low risk of miscarriage and malformation. Therefore, these drugs should only be used intermittently in the first trimester of pregnancy (GRADE 1B, SOA 97.3).

ii) Intermittent rather than regular use of all non-selective NSAIDs except LDA is recommended throughout pregnancy and weaned from end of second trimester (26 weeks) to stop by gestational week 30 to avoid premature closure of the ductus arteriosus (GRADE 1B, SOA 98).

iii) At present there are limited data on selective cyclooxygenase-2 inhibitors; they should therefore be avoided during pregnancy (GRADE 2C, SOA 98.5).

iv) Non-selective NSAIDs (especially ibuprofen) are compatible with breastfeeding (GRADE 1C, SOA 98.8).

Recommendations for LDA and clopidogrel in pregnancy and breastfeeding

i) LDA may be continued throughout pregnancy and NICE guidelines (2019) for hypertension in pregnancy advise treatment with LDA (for prophylaxis of pre-eclampsia) until delivery (GRADE 1B, SOA 99.0).

ii) LDA is compatible with breastfeeding (GRADE 2C, SOA 99.8).

iii) There are limited data on clopidogrel but it may be considered where alternative drugs are not suitable in pregnancy and breastfeeding (GRADE 2C, SOA 96.3).

Colchicine and dapsone

These drugs were not considered in the previous BSR guideline and are now included because they may be used to treat certain inflammatory rheumatic diseases. UKTIS does not report on colchicine or dapsone. A systematic review and meta-analysis of colchicine use in 550 pregnancies of women with mostly familial Mediterranean fever (FMF) at doses of 1–2 mg per day, compared with 1263 non-exposed pregnancies found this drug did not significantly increase the incidence of foetal malformations or miscarriage when taken during pregnancy [46]. However, the National Amyloidosis Centre recommends to continue the prescribed dose as there are no established safety concerns at colchicine doses >2 mg daily during pregnancy [47].

No systematic review data was identified for dapsone. A review of 924 pregnancies exposed to dapsone to treat malaria was precluded from meaningful risk-benefit analysis due to limited reporting of outcomes [48]. They concluded that the use of dapsone may be considered when no suitable alternative is available and the threat of malaria is the greater risk. It is a safe option in pregnant patients without glucose-6-phosphate dehydrogenase (G6PDH) deficiency and can be used during lactation while monitoring the baby for haemolysis and G6PDH deficiency [49]. A review of the treatment of rheumatic and autoimmune skin disease in women during pregnancy concluded that dapsone may be safely and cautiously used during pregnancy [50].

LactMed reports that long-term prophylactic maternal doses of colchicine up to 1.5 mg daily produce levels in milk that result in the infant receiving <10% of the maternal weight-adjusted dosage and no adverse effects have been reported from limited studies. It also states that the highest milk levels occur 2–4 h after a dose, so avoiding breastfeeding during this time can minimize the infant dose, or simply taking the drug after nursing. LactMed also states that dapsone can be used during breastfeeding; however, haemolytic anaemia might occur, especially in newborn infants and in those with G6PDH deficiency [20]. Recommendations for these drugs were based on evidence as shown in Supplementary Table S5, available at *Rheumatology* online.

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Recommendations for colchicine and dapsone in pregnancy and breastfeeding

i) Colchicine therapy may be considered during pregnancy (GRADE 1B, SOA 99.5).
ii) Dapsone may be used in pregnancy (GRADE 2C, SOA 95.0).
iii) Colchicine may be used in breastfeeding (GRADE 2C, SOA 98.3).
iv) Dapsone may be used in breastfeeding and due to the risk of haemolytic anaemia it is advised to monitor the infant for signs of haemolysis, especially in newborn or premature breastfed infants (GRADE 2C, SOA 90.7).

Anticoagulants in rheumatic disease

The deleterious effects of warfarin and compatibility of heparin in pregnancy are well described and evidence-based guidelines for the management of venous thromboembolism (VTE) and thrombophilia in pregnancy exist [51].

Heparin

A systematic review [41] and systematically produced guidelines [52] describe the utility of heparin in the management of VTE and pregnancy morbidity in pregnant patients with antiphospholipid syndrome (APS). Heparin/LMWH does not cross the placenta [1, 2].

Heparins are compatible with breastfeeding. There were no additional studies identified, but LactMed states that no particular caution is required as the molecular weight of heparin is such that it is unlikely to be appreciably excreted into breastmilk.

Warfarin

Warfarin has the ability to cross the placenta and is associated with an increased risk of congenital abnormalities including a characteristic warfarin embryopathy (hypoplasia of the nasal bridge, congenital heart defects, ventriculomegaly, agenesis of the corpus callosum, stippled epiphyses) in ~5% of foetuses exposed between 6 and 12 weeks of gestation. Warfarin should therefore be avoided between 6 and 12 weeks [51]. While heparin/LMWH remains the anticoagulant of choice in pregnancy for the majority of patients considered to be at increased thrombotic risk in pregnancy, warfarin may be considered in pregnancy for women with mechanical heart valves (MHVs). The LMWH regimen could be used for those who refuse warfarin and other vitamin K antagonists (VKAs) [53]. In management of atrial fibrillation, VKAs may be used after the first trimester [54].

LactMed is reassuring both with regard to low drug levels in breastmilk and infant serum, and no reported adverse effects.

New anticoagulants

A systematic review [55] identified 236 cases of direct oral anticoagulants (DOAC) use in pregnancy of rivaroxaban ($n = 178$), dabigatran ($n = 27$), apixaban ($n = 21$) and edoxaban ($n = 10$). DOACs were mostly used for prophylaxis or treatment of venous thromboembolism ($n = 91$). DOACs were discontinued within the first 2 months of pregnancy in 84%, and the maximum reported duration of use was 26 weeks. Pregnancy outcome data were available for 140 pregnancies. Thirty-nine pregnancies were electively terminated. In the remaining 101 pregnancies, total miscarriage rate was 31% ($n = 31$) and live birth rate was 68% ($n = 69$, one missing). Foetal and neonatal abnormalities were reported in eight pregnancies, of which at least half were suspected to be related to rivaroxaban use during the first trimester of pregnancy. In only 18% of cases ($n = 42$), the presence or absence of thrombotic and bleeding complications was reported. This limited evidence raises concern regarding embryo-foetal safety, with a high incidence of miscarriages and a 4% rate of congenital anomalies with the use of rivaroxaban. Overall, not enough data are available to judge safety and efficacy of the use of DOACs during pregnancy and rivaroxaban and dabigatran have both been shown to cause adverse obstetric outcomes in animal studies, described in summary of product characteristics [56, 57]. UKTIS does not report on DOACs.

LactMed describes several case reports that consistently indicate that maternal doses of rivaroxaban of 15–30 mg daily produce low levels in milk that are considerably below doses required for anticoagulation in infants [20]. Therefore, breastfeeding is not contraindicated if rivaroxaban is required by the mother. There are no data on the excretion of dabigatran into human milk.

Fondaparinux

Fondaparinux may be considered if there is an allergy or adverse response to LMWH, although solid data are lacking and minor transplacental passage has been demonstrated, without any adverse materno-foetal effects in five pregnancies [58]. LactMed considers use of fondaparinux to be acceptable during breastfeeding [20]. Recommendations on all anticoagulants were based on evidence as shown in Supplementary Table S6, available at *Rheumatology* online.

Recommendations for anticoagulants in pregnancy and breastfeeding

i) LMWH heparin is compatible throughout pregnancy (GRADE 1A, SOA 100).
ii) LMWH is compatible with breastfeeding (GRADE 1C, SOA 100).
iii) The use of warfarin in pregnancy is associated with increased foetal risk throughout pregnancy and has limited indications, therefore should only be considered in exceptional circumstances (GRADE 1B, SOA 98.8).
iv) Warfarin is compatible with breastfeeding (GRADE 1A, SOA 100).
v) Direct oral anticoagulants (DOACs) cannot be recommended in pregnancy (GRADE 1C, SOA 97.9).
vi) Rivaroxaban may be considered in breastfeeding (GRADE 2C, SOA 95.3).
vii) Other DOACs are not recommended in breastfeeding due to lack of human data and concerns from animal studies (GRADE 1C, SOA 97.4).
viii) Fondaparinux may be considered in pregnancy and breastfeeding if there is an allergy or adverse response to LMWH (GRADE 2C, SOA 95.5).

Bisphosphonates

Bisphosphonates are not ideal in women planning pregnancy because the absolute risk of fracture is small in this age group and the skeletal half-life of these drugs is very long. The number of human pregnancy exposures remains limited and a detailed literature review identified 40 pregnancies [59], while a systematic review published in abstract form described

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outcomes from 120 bisphosphonate-exposed pregnancies [60]. Overall, rates of congenital malformation and miscarriages were comparable in bisphosphonate and controls, although limiting factors included: few comparator groups; heterogeneous maternal disease; concomitant medication; and small sample size. Controlled studies have demonstrated possible associations between preconceptual/gestational bisphosphonate exposure and increased risk of spontaneous abortion, decreased infant birth weight, and lower gestational age at delivery. These findings, however, may reflect data limitations and/or uncontrolled confounding (UKTIS). Therefore, further controlled studies are required to fully establish the safety of bisphosphonates in pregnancy and they are not drugs of choice in women planning pregnancy.

LactMed states that limited evidence indicates that breastfeeding after cessation of long-term bisphosphonate treatment appears to have no adverse effects on the infant. There is no information on the use of alendronate or risedronate during breastfeeding. Limited information indicates that maternal doses of pamidronate of 30 mg intravenously produce very low levels in milk and because pamidronate has a serum half-life of ~3 h, is highly bound to calcium and poorly absorbed orally, absorption of pamidronate by a breastfed infant is unlikely. Therefore, withholding breastfeeding for 12–24 h after a dose should ensure that the breastfed infant is exposed to little or no pamidronate. If the mother receives a bisphosphonate during pregnancy or nursing, some experts recommend monitoring the infant's serum calcium during the first 2 months postpartum [20]. These recommendations were based on evidence as shown in Supplementary Table S7, available at *Rheumatology* online.

Recommendations for bisphosphonates in pregnancy and breastfeeding

i) There is insufficient data upon which to recommend bisphosphonates in pregnancy or to advise a specific time for them to be stopped pre-conception. Given their biological half-life in bone of up to 10 years and no evidence of harm from limited reports of their use in pregnancy, a pragmatic recommendation is that they should be stopped 3 months in advance of pregnancy (GRADE 2C, SOA 96.8).
ii) There are no data on which to base a recommendation for the use of bisphosphonates during breastfeeding (GRADE 2C, SOA 98.5).

Antihypertensive medication in rheumatic disease

Patients with ARD, particularly renal SLE and systemic sclerosis (SSc) frequently require anti-hypertensive treatment for sometimes life-threatening disease, such as scleroderma renal crisis, that may require specialist use of certain antihypertensive drugs. The introduction of ACEis for the treatment of SSc renal crisis has significantly reduced mortality rates of up to 50% in the 1970s to a mortality of up to 20% at 6 months after introducing ACEis. The use of ACEis may therefore be indicated (also in pregnancy) in exceptional circumstances [7].

The management of pre-existing and new onset hypertension in pregnancy has been comprehensively reviewed and updated in the 2019 NICE guideline, Hypertension in Pregnancy: Diagnosis and Management [40].

Angiotensin blockade

Disruption of the renin-angiotensin system (RAS) in pregnancy by maternal treatment with ACEis or angiotensin receptor blockers (ARBs) in the second/third trimester leads to abnormal foetal renal development, known as foetal RAS blockade syndrome [61]. There are conflicting results, however, on the risk of this fetopathy occurring after first trimester exposure. A systematic review and meta-analysis [62] of 19 articles involving 4 163 753 pregnant women found a significant association between overall congenital malformations and first trimester-only exposure to ACEis/ARBs (odds ratio 1.94; 95% CI 1.71, 2.21; $P < 0.0001$). This review also found a significant association between cardiovascular malformations, miscarriage and stillbirth and ACEi/ARB exposure. A similar risk was observed in a cohort of 1 333 624 pregnancies [63], including 4107 (0.31%) following first trimester ACEi exposure that found an increased risk of overall malformations in the ACEi-exposed pregnancies [unadjusted relative risk (RR), 1.82; 95% CI 1.61, 2.06] and of cardiac malformations (RR 2.95; 95% CI 2.50, 3.47). On further analysis, however, restricting the cohort to pregnancies complicated by chronic hypertension (both exposed and unexposed) and accounting for other confounding factors, there was no significant increase in the risk of any of the outcomes assessed.

NICE guidelines state that women taking ACEis/ARBs should be advised of the increased risk of congenital anomalies if these drugs are taken during pregnancy and to discuss alternative antihypertensive drugs with their clinician responsible for managing their condition [40]. If they become pregnant on ACEis/ARBs they should be stopped (preferably within 2 working days of notification) and other antihypertensive treatments offered. UKTIS recommends that where prolonged first trimester exposure has occurred, a 20-week anomaly scan should focus on cardiovascular, renal and neurological development, in addition to the routine anatomical checks. UKTIS states that ACEi fetopathy following exposure to ACEis in the second and third trimesters of pregnancy is well-described and may include oligohydramnios, renal tubular dysgenesis, neonatal anuria, hypocalvaria, pulmonary hypoplasia, persistent patent ductus arteriosus, mild-to-severe intrauterine growth restriction, and foetal or neonatal death. It is proposed that these effects occur as a result of a direct effect on the foetal RAS which begins to function from ~26 weeks gestation. A small prospective case series has suggested that the risk period for ACEi fetopathy is with exposure beyond 20 weeks gestation. Due to data limitations, the absolute risk of ACEi fetopathy is unclear. Due to the risk of ACEi fetopathy, use of ACEis in the second and third trimesters is generally contraindicated and should only be reserved for cases of severe maternal illness that cannot be managed using alternative drugs [18].

Negligible amounts of enalapril and captopril are transferred into breastmilk with no adverse effects reported on the breastfed infants of mothers treated with short-acting ACEis [64]. NICE states that enalapril may be offered to treat hypertension in breastfeeding mothers with appropriate monitoring of maternal renal function and serum potassium [40]. The following recommendations were based on evidence as shown in Supplementary Table S8, available at *Rheumatology* online.

Recommendations for ACEis/ARBs in pregnancy and breastfeeding

i) ACEis and ARBs should be stopped as soon as possible when pregnancy is confirmed in the first trimester and if

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necessary an alternative antihypertensive compatible with pregnancy given (GRADE 1A, SOA 100).
ii) ACEis/ARBs should be avoided in the second and third trimester but may be considered under specialist advice in certain circumstances (GRADE 1C, SOA 98.5).
iii) Based on limited evidence, enalapril is compatible with breastfeeding (GRADE 2C, SOA 98.5).

Calcium channel blockers

Calcium channel blockers (CCBs) including amlodipine, diltiazem, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil are mainly used for the treatment and prophylaxis of angina, and the treatment of hypertension where an ACEi/ARB is unsuitable. In patients with rheumatic disease, nifedipine or amlodipine are also used to treat Raynaud's phenomenon.

UKTIS has not identified an increased risk of congenital malformations or other adverse pregnancy outcomes with CCBs, although data remains too limited to draw firm conclusions on many outcomes. Data on rates of preterm delivery, foetal growth and neurodevelopmental outcomes are too limited and/or confounded to permit an accurate risk assessment, but where a CCB is required to treat maternal hypertension or as a tocolytic, foetal benefits of use are likely to outweigh any unspecified risk and treatment should not be withheld on this basis [18]. Data is more limited for amlodipine so it is not included in alternatives to treat hypertension in pregnancy that include labetalol, nifedipine or methyldopa in order of preference [40].

LactMed describes low levels of nifedipine and amlodipine in breastmilk, without any adverse effects being reported among exposed infants [20]. NICE guidance of other antihypertensive drugs that may be offered in breastfeeding mothers include nifedipine, amlodipine, atenolol or labetolol [40]. Recommendations were based on evidence as shown in Supplementary Table S8, available at *Rheumatology* online.

Recommendations for CCBs in pregnancy and breastfeeding

i) Nifedipine is compatible with pregnancy with no direct evidence of harm at doses up to 90 mg/day (GRADE 1A, SOA 99.0).
ii) Nifedipine is compatible with breastfeeding (GRADE 1B, SOA 100).
iii) Amlodipine can be considered in pregnancy and breastfeeding as there is no evidence of harm (GRADE 1C, SOA 97.9).

Pulmonary vasodilators

Moderate-to-severe pulmonary hypertension (PHT) is a rare complication of certain ARDs and remains a contraindication to planned pregnancy with high mortality. Unintentional pregnancy and/or patient choice, however, means that treatment of this condition with specific pulmonary vasodilators may be required in pregnancy. Limited information on use of these drugs in human pregnancy was identified in the previous BSR guideline [2]. No studies were identified examining pregnancy outcomes after paternal exposure to any of these pulmonary vasodilators.

Sildenafil

Sildenafil has been studied in the context of trying to improve utero-placental circulation in pregnancies affected by severe foetal growth restriction. A systematic review and meta-analysis were identified, examining the utility of sildenafil being used for treatment or prevention of obstetric diseases compared with placebo. They analysed 598 pregnant women from seven clinical trials with pre-eclampsia ($n = 139$), intrauterine growth restriction ($n = 275$) and oligohydramnios ($n = 184$) and found a significant improvement in birthweight following sildenafil treatment during pregnancy, with no difference in other outcomes [65].

However, in 2018 a randomised controlled study looking at using sildenafil to treat pregnant women in whom there was significant foetal growth restriction was halted early due to a number of neonates having persistent pulmonary hypertension of the newborn (PPHN). This multi-centered study enrolled women with a singleton pregnancy between 18 and 30 weeks with severe foetal growth restriction of likely placental origin, where the likelihood of perinatal death/severe morbidity was estimated to be significant. Participants were randomised into sildenafil or placebo arms. One of three study sites reported that PPHN appeared to be more prevalent in infants exposed *in utero* to sildenafil compared with placebo-exposed infants ($n = 17/93$ *vs* $n = 3/90$), that death among infants with PPHN was more common following sildenafil exposure ($n = 11/17$ *vs* $n = 0/3$), and that when the overall neonatal death rate was considered, there was a non-statistically significant trend towards an increased risk following sildenafil exposure ($n = 19/93$ *vs* $n = 9/90$). As a result, the trial was halted early and sildenafil is no longer recommended to improve placental function in severely growth-restricted babies [66, 67].

However, it should be noted that two further study sites for this trial did not detect an increased risk of PPHN and overall, this trial has not identified a clear beneficial effect of sildenafil on foetal outcome. PPHN is more prevalent in premature and growth-restricted foetuses and is a relatively rare complication in healthy babies delivered at term.

UKTIS recommends that general use of sildenafil in pregnancy should be avoided where possible [18]. However, in the context of maternal pulmonary hypertension there is clear benefit in the use of sildenafil to reduce the effects of pulmonary hypertension, which often gets worse during pregnancy. Case studies/case series data suggest that sildenafil exposure was not associated with miscarriage or congenital anomaly; however, the data is extremely limited (around 18 reported pregnancies). The risks and benefits of continuing sildenafil should be discussed with the patients, but most will likely require ongoing treatment.

LactMed describes limited data showing that sildenafil and its active metabolite are poorly excreted into breastmilk and amounts ingested by the infant are small and would not be expected to cause any adverse effects in breastfed infants [20].

Bosentan

Animal data have revealed teratogenicity due to bosentan, including malformations of the head, mouth, face and large blood vessels in addition to an increased number of stillbirths and increased mortality [68]. Previously, we identified data from 12 pregnancies of women with PHT treated with bosentan in pregnancy plus multiple other medications, including sildenafil and iloprost, with reduced pregnancy duration of 37 weeks in one and reduced birth weight in two cases but no other maternal complications or foetal loss [2]. We identified one further case report of a patient with Eisenmenger

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syndrome exposed to long-term bosentan before and during pregnancy that was delivered by caesarean section at 27 weeks due to severe maternal PHT without any evidence of teratogenic effects of bosentan [69]. UKTIS does not report on bosentan.

LactMed states there is little published experience with bosentan during breastfeeding and an alternate drug may be preferred, especially while nursing a newborn or preterm infant [20].

Prostacyclines

Previously we identified data on 23 pregnancies of patients with PHT (three with SLE) treated with iloprost ($n = 5$ pregnancies) or epoprostenol ($n = 15$ pregnancies) and three other prostacyclines (unspecified type) in patients who were taking multiple other medications, including immunosuppressants, sildenafil and bosentan [2]. Findings of premature deliveries and reduced birthweight were confounded by maternal disease. Furthermore, maternal complications were attributable to PHT. We did not identify any new evidence and UKTIS and LactMed do not report on iloprost or epoprostenol. The recommendations were based on evidence as shown in Supplementary Table S7, available at *Rheumatology* online.

Recommendations for pulmonary vasodilators in pregnancy and breastfeeding

i) Established moderate to severe PHT remains a contraindication to pregnancy. If pregnancy occurs, the use of these pulmonary vasodilator drugs in pregnancy should be considered only as part of a multidisciplinary team assessment (GRADE 1C, SOA 99.5).
ii) Limited evidence supports the use of prostacyclines to treat PHT during pregnancy (GRADE 2C, SOA 98.0).
iii) Limited evidence supports the use of sildenafil to treat PHT during pregnancy (GRADE 2C, SOA 98.0).
iv) Bosentan is teratogenic in animals and although there is no evidence of harm from human pregnancy, the evidence is insufficient to recommend in pregnancy (GRADE 1C, SOA 98.8).
v) There are no data relating to breastfeeding exposure to pulmonary vasodilators on which to base a recommendation (GRADE 2C, SOA 98.8).

Paternal exposures

There remains limited data on paternal exposure to drugs used to treat rheumatic disease and reports of teratogenic effects linked with paternal exposure are lacking for all drugs considered in this guideline. Our updated search revealed the following additional information.

Links with adverse neurodevelopmental outcomes [70] but not asthma [71] have been reported following paternal exposure to paracetamol from the largest cohort study of paracetamol in pregnancy. A direct causal effect, however, remains unproven.

An observational prospective cohort study from Sweden [72] of 3983 children born to fathers receiving antidepressant treatment around conception, included fathers treated with: SSRIs, $n = 2865$; SNRIs, $n = 470$; and TCAs, $n = 240$. This study found paternal intake of all antidepressants studied to be safe with respect to the risk of preterm birth, malformation, autism or intellectual disability.

A systematic review of the effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes [73] found very weak evidence of reduced sperm parameters with codeine, tramadol and CCBs but not NSAIDs, LDA or ACEi and no abnormalities in offspring were reported for any drug. Interestingly, low-dose lisinopril (2.5 mg/day) has been shown to increase total sperm count and motility in a randomised, controlled, crossover pilot of study of normotensive men with idiopathic oligospermia leading to an unassisted pregnancy rate of 48.5% [74]. Small studies of chronic use of NSAIDs in men with rheumatic disease have not indicated any impairment of spermatogenesis and no evidence for harmful effects of NSAIDs on offspring [75].

A systematic review [76] of eight studies including 166 cases of paternal exposure found inconsistent reports of adverse effects of colchicine on sperm quality and only one study ($n = 53$) of paternal exposure did not find an adverse effect on offspring [77].

The following recommendations were based on evidence as shown in Supplementary Table S9, available at *Rheumatology* online.

Recommendations for paternal exposure

i) Paracetamol is compatible with paternal exposure (GRADE 1B, SOA 98.5).
ii) Amitriptyline, SNRIs and SSRIs are compatible with paternal exposure (GRADE 1B, SOA 98.5).
iii) Non-selective NSAIDs are compatible with paternal exposure (GRADE 1C, SOA 98.4).
iv) Based on limited or no data and no association with adverse foetal development or pregnancy outcome, paternal exposure to all other drugs described in this guideline are unlikely to be harmful (GRADE 2C, SOA 97.3).

Applicability and utility

Implementation

Awareness of these guidelines will aid clinical practitioners and patients in decision making and will be raised through presentation at local, regional and national meetings. No barriers to implementation of these guidelines are anticipated.

Key standards of care

Patients with rheumatic disease should receive tailored pre-pregnancy counselling and then be reviewed during pregnancy and the four month post-partum period by clinical practitioners with expertise in the management of rheumatic disease in pregnancy, in addition to their routine obstetric care. They should have access to written information on relevant medications in pregnancy and breastfeeding that is accurate and allows them to make informed decisions regarding compatibility of certain drugs in pregnancy.

Future research agenda

The limitation of current evidence highlights the need for a national pregnancy registry for patients with rheumatic disease, as currently exists for women with epilepsy. All women with rheumatic disease who become pregnant would be eligible to register, whether or not they are on anti-rheumatic treatment. The prospective pregnancy outcome data would then be published to display information on outcomes such as miscarriage and congenital anomalies in patients treated with

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anti-rheumatic and other drug therapy. These data would also be used to answer specific questions where data is currently lacking. Data relating to the impact of paternal exposure to these drugs (both fertility and male-mediated teratogenicity), as well as breastfeeding exposure is particularly limited, and further research in these areas is urgently required.

Mechanism for audit of the guideline

An audit pro forma to assess compliance with these guidelines is shown in Supplementary Data S1, available at *Rheumatology* online.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability statement

All relevant data produced during the guideline development process are presented in the guideline or in the accompanying supplementary material.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: All authors have made declarations of interest in line with BSR policy (see Supplementary Material, available at *Rheumatology* online). L.M. has received honoraria from UCB and educational funding support from Abbvie and Pfizer. C.G. has received honoraria from Abbvie, Alumis, Amgen, Astra-Zeneca, MGP, Sanofi and UCB. C-S.Y. has received honoraria from Amgen. K.S. has received educational support from UCB and honoraria from UCB and Thermo-Fisherworks and Novo Nordic Foundation research grant. L.W. has received honorarium from Novartis. M.D.R. has received educational funding support from Lilly, Pfizer, Janssen and UCB and honoraria from Lilly, Menarini and Biogen. S.T. has received honoraria from UCB. I.G. has received honoraria and unrestricted research grants from UCB. K.H. has received honoraria and educational support from UCB. M.G. has received honoraria from UCB, Lily and Abbvie. M.K. is an employee of GSK and gave independent expert advice to the working group. The remaining authors have declared no conflicts of interest.

Acknowledgements

A full list of Standards, Audit and Guidelines Working Group members can be found in Supplementary Data S2, available at *Rheumatology* online. All contributing members are named in the authorship list.

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Arthritis & Rheumatology
Vol. 72, No. 4, April 2020, pp 529–556
DOI 10.1002/art.41191
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2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases

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Objective. To develop an evidence-based guideline on contraception, assisted reproductive technologies (ART), fertility preservation with gonadotoxic therapy, use of menopausal hormone replacement therapy (HRT), pregnancy assessment and management, and medication use in patients with rheumatic and musculoskeletal disease (RMD).

Methods. We conducted a systematic review of evidence relating to contraception, ART, fertility preservation, HRT, pregnancy and lactation, and medication use in RMD populations, using Grading of Recommendations Assessment, Development and Evaluation methodology to rate the quality of evidence and a group consensus process to determine final recommendations and grade their strength (conditional or strong). Good practice statements were agreed upon when indirect evidence was sufficiently compelling that a formal vote was unnecessary.

Results. This American College of Rheumatology guideline provides 12 ungraded good practice statements and 131 graded recommendations for reproductive health care in RMD patients. These recommendations are intended to guide care for all patients with RMD, except where indicated as being specific for patients with systemic lupus erythematosus, those positive for antiphospholipid antibody, and/or those positive for anti-Ro/SSA and/or anti-La/SSB antibodies. Recommendations and good practice statements support several guiding principles: use of safe and effective contraception to prevent unplanned pregnancy, pre-pregnancy counseling to encourage conception during periods of disease quiescence and while receiving pregnancy-compatible medications, and ongoing physician-patient discussion with obstetrics/gynecology collaboration for all reproductive health issues, given the overall low level of available evidence that relates specifically to RMD.

Conclusion. This guideline provides evidence-based recommendations developed and reviewed by panels of experts and RMD patients. Many recommendations are conditional, reflecting a lack of data or low-level data. We intend that this guideline be used to inform a shared decision-making process between patients and their physicians on issues related to reproductive health that incorporates patients' values, preferences, and comorbidities.

INTRODUCTION

The management of reproductive health issues in patients with rheumatic and musculoskeletal diseases (RMD) differs from that in healthy persons. As a result, rheumatologists and other clinicians caring for these patients must often discuss with and counsel their patients about contraception, pregnancy and lactation (including medications), assisted reproductive technology (ART), fertility preservation, and hormone replacement therapy (HRT), and they must collaborate with specialists in the fields of obstetrics-gynecology, maternal-fetal medicine, and reproductive endocrinology and infertility.

Pregnancy in women with RMD may lead to serious maternal or fetal adverse outcomes; accordingly, contraception, tailored to the individual patient with emphasis on safety and efficacy, should be discussed and encouraged. Because risk for pregnancy complications depends on diagnosis, disease activity and damage, medications, and the presence of anti-Ro/SSA, anti-La/SSB, and antiphospholipid (aPL) antibodies, pre-pregnancy assessment is critical to informing pregnancy management, therapy, and outcomes. The ability to become pregnant may itself be an independent concern for some patients, so minimizing risk of gonadal insufficiency is important. RMD patients with subfertility value advice from their rheumatologists about oocyte preservation and in vitro fertilization (IVF).

It is difficult to avoid use of medication during pregnancy in patients with RMD. Not all medications are safe for preconception use by men and women or during pregnancy and lactation, but uncontrolled systemic inflammatory disease is itself associated with poor pregnancy outcomes (1–6). In addition, patients are vulnerable to disease flare postpartum (7,8), but the American Academy of Pediatrics recommends that infants be exclusively breastfed for 6 months (9). In many cases medication safety is uncertain because most data are derived from case reports, small series, and observational studies; direct data from randomized controlled trials are scarce. As a result, identifying the appropriate screening and management (including medication use) for RMD patients is challenging for clinicians.

Given the primary goal of providing recommendations for care of all adult RMD patients throughout the reproductive lifespan, the scope of this guideline is broad. There has been little attention to aspects of reproductive health care other than pregnancy in patients with RMD, and the American College of Rheumatology (ACR) recognizes the imperative for guidance in reproductive health issues for these patients.

This article is published simultaneously in *Arthritis Care & Research.*
Supported by the American College of Rheumatology.

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Dr. Bermas has received consulting fees, speaking fees, and/or honoraria from UCB (less than $10,000). Dr. Chakravarty has received consulting fees, speaking fees, and/or honoraria from UCB (less than $10,000). Dr. Chambers has received research support from Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Pfizer, Regeneron, Hoffmann La-Roche-Genentech, Genzyme-Sanofi-Aventis, Seqirus, Takeda Pharmaceuticals, UCB, Sun Pharma Global FZE, and the Gerber Foundation. Dr. Clowse has received consulting fees, speaking fees, and/or honoraria from AstraZeneca and MotherToBaby (less than $10,000 each) and from UCB (more than $10,000) and research support from GlaxoSmithKline (paid to Duke University). Dr. Lockshin has received consulting fees, speaking fees, and/or honoraria from Advance Medical, groupH, Biologische Heilmittel Heel, and Defined Health and has served as an expert witness concerning adverse pregnancy outcome with question of antiphospholipid syndrome. Dr. Branch has received research support from UCB. Dr. Laskin has received consulting fees, speaking fees, and/or honoraria from AbbVie (less than $10,000) and research support from Ferring Pharmaceuticals. Dr. Salmon has received consulting fees, speaking fees, and/or honoraria from UCB and Bristol-Myers Squibb (less than $10,000 each) and owns stock or stock options in Bristol-Myers Squibb, Abbott, Pfizer, Eli Lilly, Biogen Idec, and Regeneron. Dr. White has received consulting fees, speaking fees, and/or honoraria from AbbVie (less than $10,000). Dr. Yazdany has received consulting fees, speaking fees, and/or honoraria from Pfizer, AstraZeneca, and Eli Lilly (less than $10,000 each). Dr. Eudy has received consulting fees, speaking fees, and/or honoraria from GlaxoSmithKline (more than $10,000) and research support from GlaxoSmithKline. Dr. Jayatilleke has received consulting fees and/or honoraria from GlaxoSmithKline (less than $10,000). No other disclosures relevant to this article were reported.

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Submitted for publication July 3, 2019; accepted in revised form December 10, 2019.

METHODS

These recommendations follow the ACR guideline development process, using a systematic literature review and Grading of Recommendations Assessment, Development and Evaluation methodology (for details, see Supplementary Appendices 1, 2, and 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). When no direct data on RMD patients were available from the systematic literature review, discussion and voting were supplemented with indirect data collected in additional, less formal literature reviews (Supplementary Appendix 4, http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) performed by Core Team members (Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract); these data were not part of the systematic literature review and are listed as "not graded" in evidence tables. Results of the systematic literature review were compiled in an Evidence Report (Supplementary Appendix 6, http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

A *strong recommendation* suggests that most informed patients would choose the recommended management. While usually reflecting a higher level of evidence, it may also reflect the severity of a potential negative outcome. A *conditional recommendation* suggests that choice will vary with individual values and preferences. Conditional recommendations generally reflect a lack of data, limited data, or conflicting data that lead to uncertainty. Finally, *good practice statements* are those for which indirect evidence is sufficiently compelling that a formal vote is unnecessary. They are presented as "suggestions" rather than formal recommendations. Recommendation numbers are denoted in Supplementary Appendix 7 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) as numbers in parentheses, allowing for cross-referencing of recommendations with tables/appendices, and referencing the order in the original list (i.e., may not be consecutive in the supplementary appendix.)

RESULTS/RECOMMENDATIONS

The detailed tables of recommendations appear in Supplementary Appendix 7 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Concise recommendations within this appendix and throughout the article are grouped into categories of contraception,

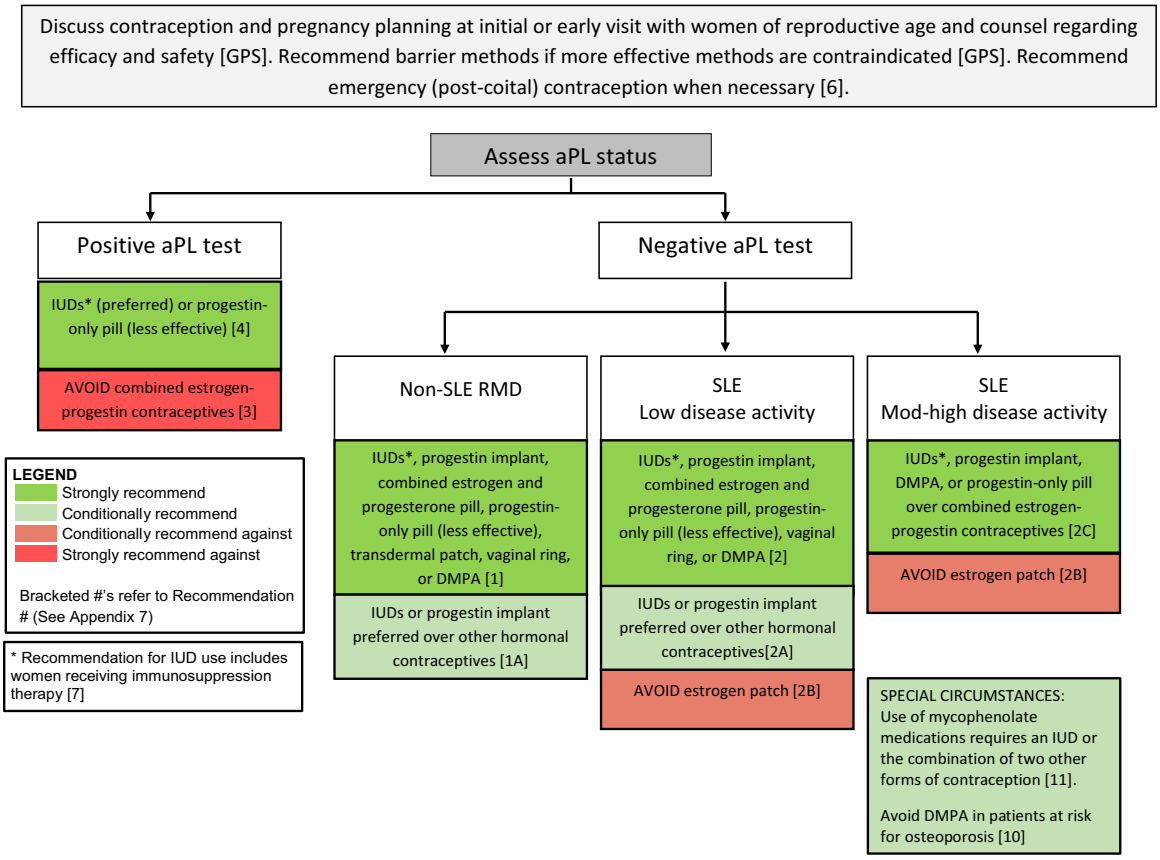
Discuss contraception and pregnancy planning at initial or early visit with women of reproductive age and counsel regarding efficacy and safety [GPS]. Recommend barrier methods if more effective methods are contraindicated [GPS]. Recommend emergency (post-coital) contraception when necessary [6].
Assess aPL status
Positive aPL test
Negative aPL test
IUDs* (preferred) or progestin-only pill (less effective) [4]
AVOID combined estrogen-progestin contraceptives [3]
Non-SLE RMD
SLE
Low disease activity
SLE
Mod-high disease activity
IUDs*, progestin implant, combined estrogen and progesterone pill, progestin-only pill (less effective), transdermal patch, vaginal ring, or DMPA [1]
IUDs or progestin implant preferred over other hormonal contraceptives [1A]
IUDs*, progestin implant, combined estrogen and progesterone pill, progestin-only pill (less effective), vaginal ring, or DMPA [2]
IUDs or progestin implant preferred over other hormonal contraceptives[2A]
AVOID estrogen patch [2B]
IUDs*, progestin implant, DMPA, or progestin-only pill over combined estrogen-progestin contraceptives [2C]
AVOID estrogen patch [2B]
LEGEND
Strongly recommend
Conditionally recommend
Conditionally recommend against
Strongly recommend against
Bracketed #'s refer to Recommendation # (See Appendix 7)
* Recommendation for IUD use includes women receiving immunosuppression therapy [7]
SPECIAL CIRCUMSTANCES:
Use of mycophenolate medications requires an IUD or the combination of two other forms of contraception [11].
Avoid DMPA in patients at risk for osteoporosis [10]

Figure 1. Recommendations and good practice statements (GPS) for use of contraception in women with rheumatic and musculoskeletal disease (RMD). aPL = antiphospholipid antibody (persistent moderate [Mod]–to-high–titer anticardiolipin or anti–β_2-glycoprotein I antibody or persistent positive lupus anticoagulant); IUDs = intrauterine devices (copper or progestin); SLE = systemic lupus erythematosus; DMPA = depot medroxyprogesterone acetate.

ART, fertility preservation with gonadotoxic therapy, use of menopausal HRT, pregnancy assessment and management, and medication use (compatibilities for paternal, maternal, and breastfeeding use are reported).

Most recommendations are general; when relevant, RMDs are specifically identified, most often for systemic lupus erythematosus (SLE) or according to presence of specific autoantibodies (aPL and anti-Ro/SSA and anti-La/SSB antibodies). In general, testing for aPL should be performed in patients with SLE or SLE-like disease and in patients with suggestive histories or physical findings; whether to check these antibodies in other RMD patients with a lower likelihood of positive results should be decided by physician-patient discussion. The presence of aPL modifies the recommendations in many circumstances, and therefore is considered separately. "Positive aPL" throughout this guideline refers to laboratory criteria only (10): persistent (2 positive test results at least 12 weeks apart) moderate-high–titer anticardiolipin antibody (aCL) (≥40 units or ≥99th percentile), moderate-high–titer anti–β_2-glycoprotein I (anti-β_2GPI) (≥40 units or ≥99th percentile), or positive lupus anticoagulant (LAC).

Detailed definitions of aPL and antiphospholipid syndrome (APS) are presented in Supplementary Appendix 8 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Briefly, included within the positive aPL group are patients with asymptomatic aPL who have no history of thrombosis or pregnancy morbidity (i.e., meet laboratory but not clinical APS criteria), patients with obstetric APS (OB APS), and patients with thrombotic APS. OB APS refers to patients who meet laboratory criteria for APS and have experienced prior pregnancy complications consistent with APS (with other causes ruled out). These include 3 consecutive losses prior to 10 weeks' gestation, a fetal loss at or after 10 weeks' gestation, or delivery at <34 weeks due to preeclampsia, intrauterine growth restriction, or fetal distress. Thrombotic APS refers to patients who meet laboratory criteria for APS and have experienced a prior thrombotic event (arterial or venous), regardless of whether they have had obstetric complications. The aPL definitions in the guideline include both patients with and patients without other underlying autoimmune disease, unless specifically stated.

Patients with lower-titer aCL and/or anti-β_2GPI (or non-criteria aPL) who do not meet laboratory classification criteria may still have some degree of risk that is difficult to quantify. Recommendations for these patients are not offered in this guideline; decisions regarding therapy rest on discussion between the patient and the physician, taking into account additional relevant risk factors.

Contraception

Supplementary Appendix 7, Table A (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations regarding contraception; strength of evidence and justifications for strong and conditional recommendations are shown in Supplementary Appendix 9 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Figure 1 details the contraception decision-making

Table 1. Safety and efficacy of various contraceptive methods in women with RMD*

Method	Safety in women with RMD	1-year failure rate, %†
Highly effective (LARC)		
Copper IUD	Safe in all women with RMD; may increase menstrual bleeding	<1
Progestin IUD	Safe in all women with RMD; may decrease menstrual bleeding	<1
Progestin implant	Limited data, but likely safe in all women with RMD	<1
Effective		
Progestin-only pill (daily)	Safe in all women with RMD; higher rate of breakthrough bleeding than with combined contraceptives; must take same time every day for efficacy	5–8
DMPA (IM injection every 12 weeks)	Safe in most women with RMD; exceptions: positive aPL, at high risk for OP	3
Combined estrogen and progesterone pill (daily)	Safe in most women with RMD; exceptions: positive aPL, very active SLE	5–8
Transdermal patch (weekly)	Safe in most women with RMD; exceptions: positive aPL, SLE; serum estrogen levels higher than with pill or vaginal ring	5–8
Vaginal ring (monthly)	Safe in most women with RMD; exceptions: positive aPL, very active SLE	5–8
Less effective		
Diaphragm	Safe in all women with RMD	12
Condom	Safe in all women with RMD; only form to prevent STD	18
Fertility awareness–based methods‡	Safe in all women with RMD; limited efficacy, especially if menses are irregular	24
Spermicide	Safe in all women with RMD; use with condoms or diaphragm to improve efficacy	28

* RMD = rheumatic and musculoskeletal disease; LARC = long-acting reversible contraception; IUD = intrauterine device; DMPA = depot medroxyprogesterone acetate; IM = intramuscular; aPL = antiphospholipid antibody; OP = osteoporosis; SLE = systemic lupus erythematosus; STD = sexually transmitted disease.
† Percent of women who will become pregnant within the first year of typical use.
‡ Methods based on the timing of the menstrual cycle.

process, and Table 1 provides efficacy data and comments on available contraceptives.

RMD patients typically underutilize effective contraception (11–13). The most important reason for effective contraception in women with RMD is to avoid risks of unplanned pregnancy, which include worsening disease activity that may threaten maternal organ function or life, adverse pregnancy outcomes (pregnancy loss, severe prematurity, and growth restriction), and teratogenesis. Members of a 1-day patient focus group, convened as part of the guideline process, emphasized their desire that clinicians caring for patients with RMD routinely discuss family planning, as they view their rheumatologists as "the doctors who know them and their medications best." We suggest that rheumatologists treating reproductive-age women with RMD discuss contraception and pregnancy plans at an initial or early visit and periodically thereafter, and always when initiating treatment with potentially teratogenic medications. One Key Question (www.powertodecide.org) has been suggested in the literature as a simple way of addressing the issue of family planning with patients: "Would you like to become pregnant in the next year?" (14). In whatever way one chooses to discuss this topic, counseling regarding contraception should include issues of efficacy and safety, with consideration of individual values and preferences.

Effectiveness of reversible forms of contraception varies. For long-acting reversible contraceptives (copper or progestin intrauterine devices [IUDs]) and subdermal progestin implants), ideal use and "real-world" use effectiveness are similar, with pregnancy rates of <1% per year ("highly effective"). Combined estrogen-progestin methods, depot medroxyprogesterone acetate (DMPA) injections, and progestin-only pills yield pregnancy rates of 3–8% per year ("effective") (15,16). Condoms, fertility-based methods (e.g., "rhythm"), and spermicide are less effective and yield pregnancy rates of 18–28% per year (17). Barrier methods confer some protection against sexually transmitted diseases.

While long-acting reversible contraceptives are encouraged as first-line contraceptives for all appropriate candidates, including nulliparous women and adolescents (17), lack of data specific to RMD and variability in clinical situations, values, and preferences may affect a patient's choice. Clinical factors that affect appropriateness of various contraceptive methods include diagnosis and activity of SLE, presence of aPL, osteoporosis, and some potentially interacting medications (see Special RMD Situations below and Supplementary Appendix 10, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). "Hormonal contraceptives" refers to any contraception containing a hormone, including estrogen-progestin contraceptives and progestin-only contraceptives. The term "fertile women" refers to women of reproductive age who do not have documented menopause, hysterectomy, or permanent sterilization (i.e., women who may become pregnant).

In fertile women with RMD who have neither SLE nor positive aPL, we strongly recommend use of effective contraceptives (i.e., hormonal contraceptives or IUDs) over less effective options or no contraception; among effective methods, we conditionally recommend the highly effective IUDs or subdermal progestin implant (long-acting reversible contraceptives) because they have the lowest failure rates.

We strongly recommend discussing use of emergency contraception with all patients, including those with SLE or positive aPL, because risks of emergency contraception are low compared to those of unplanned pregnancy.

Levonorgestrel, the over-the-counter option, is widely available and has no medical contraindications to use, including thrombophilia (18).

SLE patients. Controlled studies of estrogen-progestin contraceptives in SLE have enrolled only women with stable, low disease activity; they specifically excluded those with high disease activity and history of thrombosis (19,20). Prospective studies (evidence level moderate) in patients with stable SLE showed no increased risk of flare related to estrogen-progestin pills (19,20), and there are no data suggesting increased SLE flare risk with progestin-only pills or copper IUDs (20,21).

In SLE patients with stable or low disease activity who are not positive for aPL, we strongly recommend use of effective contraceptives (i.e., hormonal contraceptives or IUDs) over less effective options or no contraception, and we conditionally recommend the highly effective IUDs or subdermal progestin implant because they have the lowest failure rates.

We conditionally recommend *against* use of the transdermal estrogen-progestin patch in patients with SLE.

Although not directly studied in SLE patients, the transdermal estrogen-progestin patch results in greater estrogen exposure than do oral or transvaginal methods (22,23), raising concern regarding potential increased risk of flare or thrombosis.

We strongly recommend progestin-only or IUD contraceptives over combined estrogen-progestin contraception in SLE patients with moderate or severe disease activity, including nephritis, because estrogen-containing contraceptives have not been studied in SLE patients with moderate or severe disease activity.

Antiphospholipid antibody–positive patients. Presence of aPL, with or without history of clinical complications, is a contraindication to use of estrogen-containing contraceptives due the potential further increase in thrombosis risk.

We strongly recommend *against* combined estrogen-progestin contraceptives in women with positive aPL because estrogen increases risk of thromboembolism.

We strongly recommend IUDs (levonorgestrel or copper) or the progestin-only pill in women with positive aPL.

In aPL-positive patients, we do not recommend DMPA due to concern regarding thrombogenicity. We do not comment on the relatively new progestin implant due to lack of data.

The risk of venous thromboembolism (VTE) in healthy women taking combined estrogen-progestin contraceptives is 36 times higher than the baseline annual risk of 1/10,000 women (24). Although whether there is any increase in thrombosis risk with progestin-only contraception is debated, progestin-only methods are widely accepted as a lower-risk option in patients for whom estrogens are contraindicated but who still need effective contraception (18,25,26). The specific progestin and its serum level affect thrombosis risk: in healthy women taking estrogen-progestin contraceptive pills that vary progestin type but not estrogen, VTE risk odds ratios range from 2.2 to 6.6 (24). However, VTE risk in healthy women using either the progestin-only pill or the progestin IUD is not increased, with relative risks (RRs) of 0.90 (95% confidence interval [95% CI] 0.57–1.45) and 0.61 (95% CI 0.24–1.53), respectively (27). Furthermore, thrombosis frequency does not increase when progestin (levonorgestrel) IUDs are used in non-RMD patients with increased (non–aPL-associated) thrombosis risk (27–29). VTE data on the newer progestin (etonogestrel) subdermal implant are inadequate to permit recommendations (the prior progestin implant containing levonorgestrel is no longer available in the US). Very limited data on non-RMD patients suggest that injectable DMPA imparts a higher VTE risk than do other progestin-only contraceptives (RR 2.67 [95% CI1.29–5.53]), similar to that with oral estrogen-progestin contraceptives (27). For this reason, we do not include DMPA among the progestin contraceptives recommended for use in patients with positive aPL.

The copper IUD is a highly effective alternative that does not increase risk of VTE, but it may increase menstrual bleeding and cramping for several months after insertion. Progestin IUDs may decrease these symptoms (30), a potential benefit for patients receiving anticoagulation therapy.

We suggest the progestin-only pill (which is an effective, but not highly effective, contraceptive) as a low-risk alternative for patients who are unable or unwilling to use an IUD. The lack of data specific to aPL-positive patients using the progestin-only pill or IUD must be weighed against the risk of pregnancy-related VTE in the general population, which is >10 times that seen with estrogen-progestin contraceptive use. Pregnancy-related thrombosis risk in aPL-positive patients is not well quantified, but VTE risk is 197/10,000 women-years for pregnant patients with a single prothrombotic mutation and 776/10,000 women-years (31) if there are multiple prothrombotic mutations.

Other special RMD situations. Factors other than diagnosis of SLE or presence of aPL may influence the choice of contraception in women with RMD. These include use of medications and presence or risk of osteoporosis. Immunosuppressive therapy does not preclude use of any contraceptive method, but there is concern that mycophenolate-containing medications may interfere with hormonal contraceptive efficacy.

Since IUDs are the most effective contraceptive options, we strongly recommend the IUD (copper or progestin) for women with RMD who are receiving immunosuppressive therapy, despite hypothetical infection risk.

IUD-associated infection risk in RMD patients receiving immunosuppressive therapy has not been specifically studied, but studies in women with HIV show no increase (32), and IUDs are recommended for all solid organ transplant patients, including adolescents (33,34). In one arm of an SLE contraceptive trial a copper IUD was used; although the number of patients receiving immunosuppressive agents was not reported, there were no cases of pelvic inflammatory disease (20).

In women with RMD who are at increased risk for osteoporosis from glucocorticoid use or underlying disease, we conditionally recommend against using DMPA as a long-term contraceptive because data suggest that bone mineral density declines by up to 7.5% over 2 years of use in a healthy population (35).

Although there are no published data suggesting increased fracture risk, the American College of Obstetricians and Gynecologists recommends caution regarding DMPA use in women with or at increased risk for osteoporosis (17).

We conditionally recommend that women with RMD taking mycophenolate mofetil/mycophenolic acid (MMF) use an IUD alone or 2 other methods of contraception together, because MMF may reduce serum estrogen and progesterone levels (in turn reducing the efficacy of oral contraceptives).

The Mycophenolate Risk Evaluation and Mitigation Strategy program suggests use of an IUD alone (copper or progestin is not specified), or an estrogen-progestin contraceptive or the progestin implant together with a barrier contraceptive (36). It is not known whether these medications reduce efficacy of progestin IUDs, which contain varying amounts of hormone and have a largely

intrauterine effect. Other recommendations vary: while the package insert states that MMF may reduce effectiveness of oral contraceptives and use of additional barrier contraceptive methods is recommended (37), the European Medicine Agency recently updated recommendations regarding use of contraception for women taking MMF to state that "two forms of contraception are preferred but no longer mandatory"(38). Voting Panel members disagreed on the need to use additional contraceptive measures. As befits a conditional recommendation, clinicians should be aware of and discuss this hypothetical risk with their patients.

Assisted reproductive technology

Supplementary Appendix 7, Table B (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents the ART recommendations with strength of supporting evidence; detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 9 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Figure 2 details the ART decision-making process.

While fertility is typically normal in women with RMD (who have not been treated with cyclophosphamide [CYC]), it decreases with age, and ART may be needed by some RMD patients. ART techniques include ovarian stimulation, which elevates estrogen levels, IVF, and embryo transfer. Ovarian stimulation cycles for IVF generally require more aggressive stimulation than do those for intrauterine insemination; they involve surgical extraction of oocytes and IVF, followed by embryo transfer. Frozen embryo transfer does not usually require ovarian stimulation.

As is the case with any underlying significant medical disease, women undertaking ovarian stimulation must be cleared medically by the appropriate specialist. Similarly, women with APS, thrombotic or otherwise, should be cleared medically by their rheumatologist. The rheumatologist should consult with the reproductive endocrinology and infertility specialist regarding adjustments to the ovarian stimulation protocol in order to minimize the risk to the patient. Women with these underlying conditions who undergo fertility therapy should do so only in centers where the appropriate expertise is readily available.

We strongly recommend proceeding with ART if needed in women with uncomplicated RMD who are receiving pregnancy-compatible medications, whose disease is stable/quiescent, and who are negative for aPL.

Compared to the benefit of a successful pregnancy, the risk of ART for subfertile patients with RMD is low; nonetheless,

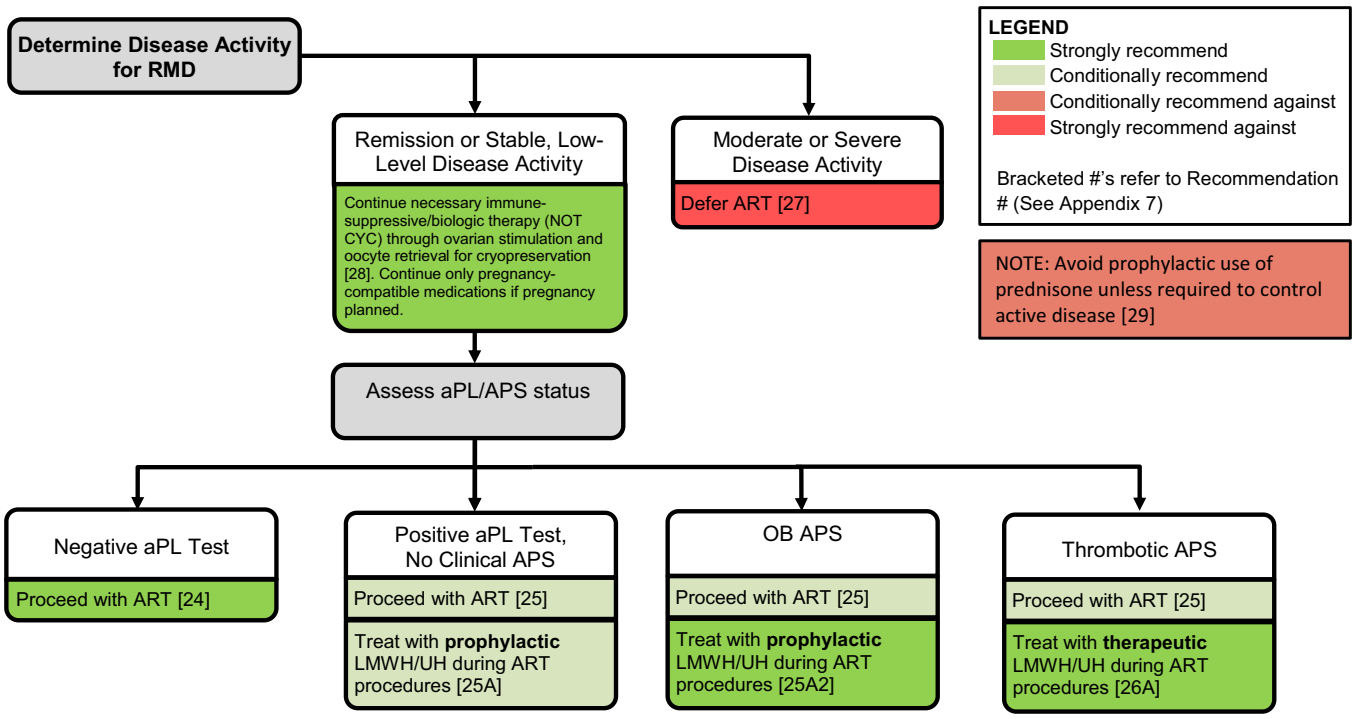
Determine Disease Activity for RMD
Remission or Stable, Low-Level Disease Activity
Continue necessary immune-suppressive/biologic therapy (NOT CYC) through ovarian stimulation and oocyte retrieval for cryopreservation [28]. Continue only pregnancy-compatible medications if pregnancy planned.
Moderate or Severe Disease Activity
Defer ART [27]
LEGEND
Strongly recommend
Conditionally recommend
Conditionally recommend against
Strongly recommend against
Bracketed #'s refer to Recommendation # (See Appendix 7)
NOTE: Avoid prophylactic use of prednisone unless required to control active disease [29]
Assess aPL/APS status
Negative aPL Test
Proceed with ART [24]
Positive aPL Test, No Clinical APS
Proceed with ART [25]
Treat with prophylactic LMWH/UH during ART procedures [25A]
OB APS
Proceed with ART [25]
Treat with prophylactic LMWH/UH during ART procedures [25A2]
Thrombotic APS
Proceed with ART [25]
Treat with therapeutic LMWH/UH during ART procedures [26A]

Figure 2. Recommendations for use of assisted reproductive technology (ART) in women with rheumatic and musculoskeletal disease (RMD). CYC = cyclophosphamide; aPL = antiphospholipid antibody (persistent moderate-to-high–titer anticardiolipin or anti–β_2-glycoprotein I antibody or persistent positive lupus anticoagulant); APS = antiphospholipid syndrome (obstetric and/or thrombotic); obstetric APS (OB APS) = patients meeting laboratory criteria for APS and having prior consistent pregnancy complications (≥3 consecutive losses prior to 10 weeks' gestation, fetal loss at or after 10 weeks' gestation, or delivery at <34 weeks due to preeclampsia, intrauterine growth restriction, or fetal distress) and with no history of thrombosis; thrombotic APS = patients meeting laboratory criteria for APS and having a prior thrombotic event (arterial or venous), regardless of whether they have had obstetric complications; LMWH = low molecular weight heparin; UH = unfractionated heparin.

risks associated with ART, especially thrombosis and lupus flare (39,40), should be discussed with patients. The level of evidence specific to RMD patients is very low (41,42), but evidence supports the safety of ART in a general population (43,44).

SLE patients. Data on IVF cycles in RMD patients are limited; however, the intended outcome of IVF, pregnancy, may be adversely affected by the presence of active RMD. In addition, there is concern that flare in SLE patients might be worsened in the setting of elevated estrogen levels.

We strongly recommend deferring ART procedures in patients with any RMD while disease is moderately or severely active; this recommendation is based on extrapolated evidence that RMD disease activity increases pregnancy risks.

For pregnancy planning, 6 months of stable inactive or low-level disease is most often suggested, but individual clinical factors may influence this decision. In patients with SLE, there is theoretical concern that ovarian stimulation with elevated estrogen levels may worsen active disease.

We conditionally recommend *against* an empiric dosage increase of prednisone during ART procedures in patients with SLE; instead, we suggest monitoring the patient carefully and treating for flare if it occurs.

No studies have evaluated prescription of prophylactic prednisone to prevent SLE flare during ART.

Antiphospholipid antibody–positive patients. Patients who are positive for aPL are at increased risk for thrombosis. Most reports of aPL-positive patients undergoing IVF describe the use of empiric prophylactic anticoagulation due to concern regarding further increased risk of potentially life-threatening thrombosis from elevated estrogen levels during ovarian stimulation.

In subfertile patients with RMD who desire pregnancy, have stable/quiescent disease, and have asymptomatic positive aPL, OB APS, or treated thrombotic APS, we conditionally recommend ART with anticoagulation, as described below.

We conditionally recommend prophylactic anticoagulation therapy with heparin or low molecular weight heparin in asymptomatic aPL-positive patients during ART procedures (41,42).

The increased risk of organ- or life-threatening thrombosis due to high estrogen levels greatly outweighs the low risk of bleeding or other complications of unfractionated heparin or low molecular weight heparin (LMWH).

We strongly recommend prophylactic anticoagulation with heparin or LMWH in women with OB APS, and we strongly recommend therapeutic anticoagulation in women with thrombotic APS, during ART procedures.

The strength of these recommendations rests on the severity of the risk of organ- or life-threatening thrombosis during ovarian stimulation. An added risk for thrombosis is ovarian hyperstimulation syndrome, an important, uncommon complication consisting of capillary leak syndrome (with pleural effusion and ascites) and, in severe cases, arterial and venous thrombosis and renal failure (43). Underlying thrombophilia increases the risk of severe ovarian hyperstimulation syndrome (44). While there are few data to guide prophylactic anticoagulation in aPL-positive patients, thromboprophylaxis is recommended to prevent thrombotic complications of moderate-to-severe ovarian hyperstimulation syndrome, as it is for patients with known inherited or acquired thrombophilia (45,46). Reports of thrombosis in aPL-positive patients undergoing IVF are uncommon, but most reported patients received empiric anticoagulation (41,42). In a recent series, 2 of 4 reported thromboses occurred in women who, on their own decision, discontinued LMWH after oocyte retrieval (41).

LMWH is used most commonly. Prophylactic dosing of enoxaparin is usually 40 mg daily, started at the beginning of ovarian stimulation, withheld 24–36 hours prior to oocyte retrieval, and resumed following retrieval. Optimal duration of prophylactic LMWH for asymptomatic aPL-positive patients undergoing ovarian stimulation has not been studied; this is a decision best made in consultation with the reproductive endocrinology and infertility specialist. The treatment is often continued until estrogen levels return to near-physiologic levels if no pregnancy occurs. Patients with OB APS will continue therapy throughout pregnancy. Aspirin is not commonly used prior to oocyte retrieval (it will be started after retrieval if indicated) given concern that its prolonged action may increase bleeding risk at the time of the retrieval. Patients receiving regular anticoagulation therapy with vitamin K antagonists for thrombotic APS should transition to therapeutic-dose LMWH for ART (usually enoxaparin 1 mg/kg subcutaneously every 12 hours), with this treatment withheld for retrieval and resumed subsequently, to continue throughout pregnancy. Since ovarian stimulation protocols vary, discussion with the reproductive endocrinology and infertility specialist is appropriate. In addition to anticoagulation, patients at risk for thrombosis or ovarian hyperstimulation syndrome may benefit from ovarian stimulation protocols that yield lower peak serum estrogen levels, such as those incorporating aromatase inhibitors (47).

Embryo and oocyte cryopreservation. Embryo and oocyte cryopreservation are good options to preserve fertility in patients whose condition is stable enough for them to undergo ovarian stimulation but who are either not able or not ready to pursue pregnancy at the time of stimulation. A carefully monitored ovarian

stimulation/IVF cycle followed by embryo transfer to a surrogate is an option, if available, for patients with severe disease-related damage who desire a biologic child and are able to undergo ovarian stimulation and oocyte retrieval, but cannot safely undergo pregnancy.

We strongly recommend continuation of necessary immunosuppressive and/or biologic therapies (except CYC, which directly impacts maturing follicles) in treated patients whose condition is stable, when the purpose of ovarian stimulation is oocyte retrieval for oocyte or embryo cryopreservation.

This includes continuation of mycophenolate or methotrexate (MTX). There is an anticipated risk of uncontrolled disease from withdrawal of effective medication. However, there are no published data that directly address oocyte retrieval during treatment with most immunosuppressive or biologic therapies other than CYC.

Fertility preservation with cyclophosphamide

Supplementary Appendix 7, Table C (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents the formal recommendations regarding fertility preservation with CYC treatment and strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 9 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

Fertility preservation in women with RMD treated with CYC. Although CYC is used less frequently than in the past due to availability of alternative treatments, it remains a mainstay of therapy for severe or life-threatening RMD. Ovarian insufficiency is a potential long-term complication of monthly intravenous CYC therapy. Hormonal co-therapy during the course of CYC is suggested to reduce risk of ovarian insufficiency.

To prevent inducing primary ovarian insufficiency in premenopausal women with RMD receiving monthly intravenous CYC, we conditionally recommend monthly gonadotropin-releasing hormone agonist co-therapy.

Ovarian insufficiency risk with CYC treatment depends on patient age and cumulative monthly CYC dose (48); measures of ovarian function remained stable during treatment according to the Euro-Lupus protocol (49). The recommendation of gonadotropin-releasing hormone agonist therapy for ovarian protection during monthly CYC therapy is based on evidence supporting benefit in early breast cancer (50,51); evidence more specific to RMD patients is less robust but positive, with limited clinical trials of gonadotropin-releasing hormone agonist (usually leuprolide acetate) that included patients with SLE and other RMD populations and used a number of different outcome measures (52–56).

Thus far, studies have addressed gonadotropin-releasing hormone agonist co-therapy only in CYC-treated RMD patients who receive CYC monthly by intravenous administration. Acknowledging this lack of data on oral CYC–treated patients, it is reasonable to consider gonadotropin-releasing hormone agonist use for these patients. Theoretically, gonadotropin-releasing hormone agonist co-therapy may not be necessary for patients receiving the lower cumulative CYC dose in the Euro-Lupus regimen (49). Expense including insurance coverage issues and difficulty coordinating administration (preferred timing is 10–14 days prior to CYC administration) may impact the ability to administer gonadotropin-releasing hormone agonist for the first CYC infusion, especially in the setting of urgent need for therapy.

Fertility preservation in men with RMD treated with CYC. CYC may cause infertility and long-term gonadal damage in treated men. Options for fertility preservation should be presented to male patients in whom CYC therapy is required.

We conditionally recommend *against* testosterone co-therapy in men with RMD receiving CYC, as it does not preserve fertility in men undergoing chemotherapy for malignancy (57).

Because sperm cryopreservation prior to treatment preserves a man's ability to conceive a healthy child, we strongly suggest sperm cryopreservation as good practice for CYC-treated men who desire it.

We acknowledge the difficulty of coordinating sperm banking when CYC therapy is urgently indicated. Because CYC causes the most damage to the postmeiosis spermatids and sperm developing during therapy have the highest degree of genetic damage (58), sperm should be collected prior to CYC treatment. If sperm is collected after CYC treatment, urologists recommend waiting a minimum of 3 months after completion of therapy (59).

Menopause and hormone replacement therapy

Supplementary Appendix 7, Table D (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations regarding menopause and HRT with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 9 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Figure 3 details the HRT decision-making process. In this guideline, postmenopausal women include women with surgically induced menopause.

Current population recommendations (60–62) suggest limiting HRT use in healthy postmenopausal women and using the lowest dose that alleviates symptoms for the minimum time necessary. Studies of long-term HRT show that risks, including stroke and breast cancer, outweigh benefits (63). Risks of HRT

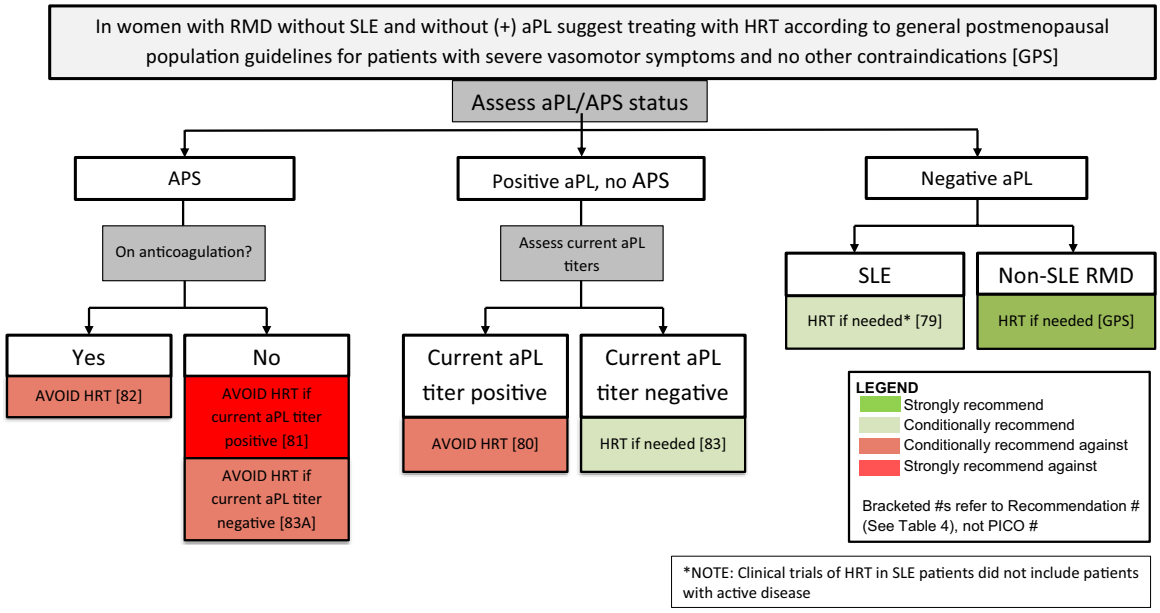
In women with RMD without SLE and without (+) aPL suggest treating with HRT according to general postmenopausal population guidelines for patients with severe vasomotor symptoms and no other contraindications [GPS]
Assess aPL/APS status
APS
Positive aPL, no APS
Negative aPL
On anticoagulation?
Assess current aPL titers
SLE
Non-SLE RMD
HRT if needed* [79]
HRT if needed [GPS]
Yes
No
Current aPL titer positive
Current aPL titer negative
AVOID HRT [82]
AVOID HRT if current aPL titer positive [81]
AVOID HRT if current aPL titer negative [83A]
AVOID HRT [80]
HRT if needed [83]
LEGEND
Strongly recommend
Conditionally recommend
Conditionally recommend against
Strongly recommend against
Bracketed #s refer to Recommendation # (See Table 4), not PICO #
*NOTE: Clinical trials of HRT in SLE patients did not include patients with active disease

Figure 3. Recommendations and good practice statements (GPS) for hormone replacement therapy (HRT) use in postmenopausal women with rheumatic and musculoskeletal disease (RMD). SLE = systemic lupus erythematosus; aPL = antiphospholipid antibody (persistent moderate-to-high–titer anticardiolipin or anti–β_2-glycoprotein I antibody or persistent positive lupus anticoagulant); APS = antiphospholipid syndrome (obstetric and/or thrombotic); PICO = population, intervention, comparator, outcomes.

depend on the type, dose, route of administration, duration of use, and timing of initiation. Benefit-risk balance is most favorable for severe vasomotor symptoms in women ≤60 years old or within 10 years of menopause onset (61).

Vasomotor symptoms, as defined by the North American Menopause Society, include hot flashes and night sweats. Hot flashes are recurrent, transient episodes of flushing, perspiration, and a sensation ranging from warmth to intense heat on the upper body and face, sometimes followed by chills. Night sweats are hot flashes that occur with perspiration during sleep (64). General contraindications to use of HRT include history of breast cancer, coronary heart disease, previous venous thromboembolic event or stroke, or active liver disease.

We strongly suggest as good practice the use of HRT in postmenopausal women with RMD without SLE or positive aPL who have severe vasomotor symptoms, have no contraindications, and desire treatment with HRT.

SLE patients. Use of HRT in symptomatic postmenopausal SLE patients may raise concerns regarding increased risk of flare and/or thrombosis; however, HRT use in aPL-negative women with quiescent SLE may be considered.

In SLE patients without positive aPL who desire HRT due to severe vasomotor symptoms and have no contraindications, we conditionally recommend HRT treatment.

Moderate-quality direct evidence supports use of oral HRT in aPL-negative women with SLE who have stable low-level disease activity and no contraindication to use (65–68), although no studies have directly addressed use of HRT in patients with moderate-to-high disease activity. The recommendation is conditional because there was a small increase in risk of mild-to-moderate (but not severe) lupus flares with use of oral HRT in the Safety of Estrogens in Lupus Erythematosus National Assessment study (65), and because the studies did not include women with active disease.

aPL-positive patients. Estrogen use in aPL-positive patients should be avoided due to the potential increased risk of thrombosis. Data are limited, however, for many clinical situations, and specific recommendations vary in strength for this reason.

In women with asymptomatic aPL, we conditionally recommend *against* treating with HRT.

We strongly recommend *against* use of HRT in women with obstetric and/or thrombotic APS.

We conditionally recommend *against* HRT use in patients with APS who are receiving anticoagulation treatment and in patients with APS who are currently negative for aPL.

We conditionally recommend consideration of HRT, if desired, in women who have a history of positive aPL but are currently testing negative for aPL and have no history of clinical APS.

Risk of VTE may be increased with HRT use in the general population (69,70). Types of estrogen and progestin and route of administration (71–74) affect risk. In the Women's Health Initiative study, VTE risk with oral estrogen-progestin increased 2-fold over placebo (70), and oral HRT in patients with factor V Leiden or prothrombin G20210A mutations increases VTE risk 25-fold compared to mutation-free women not receiving HRT (75,76). In contrast, recent studies show that transdermal estrogen does not increase VTE risk in healthy women (71,74), even those with prothrombotic mutations or high body mass index (75,77). No studies, however, have specifically assessed thrombosis risk with oral or transdermal HRT in women with aPL.

Direct evidence regarding thrombosis risk with HRT in SLE patients with or without aPL is low, as studies have addressed risk of flare in SLE but not thrombosis, and some studies excluded patients with prior thrombosis (65,67). In one study 106 SLE patients, regardless of aPL status but excluding those with recent thrombosis, were randomized to receive oral estrogen-progestin HRT or placebo. Approximately one-third of the patients in each group had some degree of positivity for aPL (level unreported) (78). During 24 months of follow-up 3 thrombotic events occurred in the HRT group and 1 in the placebo group, a nonsignificant difference.

Available evidence supports the use, when indicated and desired, of HRT in RMD patients without aPL, including those with SLE (65). Given the demonstrated lower VTE risk with transdermal administration as opposed to oral estrogen-progestin preparations even in women at increased prothrombotic risk (77), it may be reasonable to consider transdermal estrogen as initial therapy.

Pregnancy: general assessment, counseling, and management

Obstetrics-gynecology or maternal-fetal medicine specialists necessarily assume primary medical management of pregnancy in a woman with RMD. An understanding of basic pregnancy physiology is helpful for rheumatologists to identify and treat active disease during pregnancy and coordinate care with obstetric providers.

Pregnancy changes may impact manifestations of RMD. Pregnancy-related increased intravascular volume may worsen already abnormal cardiac or renal function. The expected 50% increase in glomerular filtration rate during pregnancy may worsen preexisting stable proteinuria. Pregnancy-induced hypercoagulability increases RMD-associated thrombosis risk. The calcium demand of fetal bone development and breastfeeding may worsen maternal osteoporosis. In addition, normal pregnancy symptoms such as malar erythema, chloasma gravidarum, anemia, elevated erythrocyte sedimentation, and diffuse arthralgias may falsely mimic symptoms of active RMD. Pregnancy-induced hypertension syndromes (preeclampsia) may be confused with lupus nephritis, scleroderma renal crisis, or vasculitis flare. HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) or eclampsia may resemble severe disease flare. Distinguishing among these syndromes requires the expertise of rheumatologists and obstetrics-gynecology or maternal-fetal medicine physicians working together.

Most information regarding pregnancy management in RMD comes from observational studies, primarily in patients with SLE and APS. There have been very few controlled trials. Data about pregnancies in rare rheumatic diseases usually derive from small case series. For these reasons, many recommendations are conditional, supported by collective experience of the Voting Panel members and patient input. Supplementary Appendix 7, Table E (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations regarding pregnancy in patients with RMD with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 11 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Figure 4 details the pregnancy management process in patients with RMD. Supplementary Appendix 10 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) provides assessment and management suggestions for specific RMDs.

As standard good practice, we strongly suggest counseling women with RMD who are considering pregnancy regarding the improved maternal and fetal outcomes (based on many studies) associated with entering pregnancy with quiescent/low activity disease (75,77,79–98). As additional good practice, we suggest maintaining concurrent care with specialists in obstetrics-gynecology, maternal-fetal medicine, neonatology, and other specialists as appropriate.

Patient participants expressed a strong desire that their physicians discuss family planning "early and often," including before planning of pregnancy. Discussion with patients should include information on medications and impact of disease activity, autoantibodies, and organ system abnormalities on maternal and fetal health. In rare situations with significant disease-related damage, such as pulmonary arterial hypertension, renal dysfunction, heart failure, or other severe organ damage, pregnancy may be contraindicated due to high risk of maternal morbidity and mortality.

In women with RMD planning pregnancy who are receiving medication that is incompatible with pregnancy, we strongly recommend switching to a pregnancy-compatible medication and observing for sufficient time to assess efficacy and tolerability of the new medication.

There are no data to support a specific period of time for observation with pregnancy-compatible medications. Timing will vary depending on individual clinical factors; in clinical practice this is usually a minimum of several months.

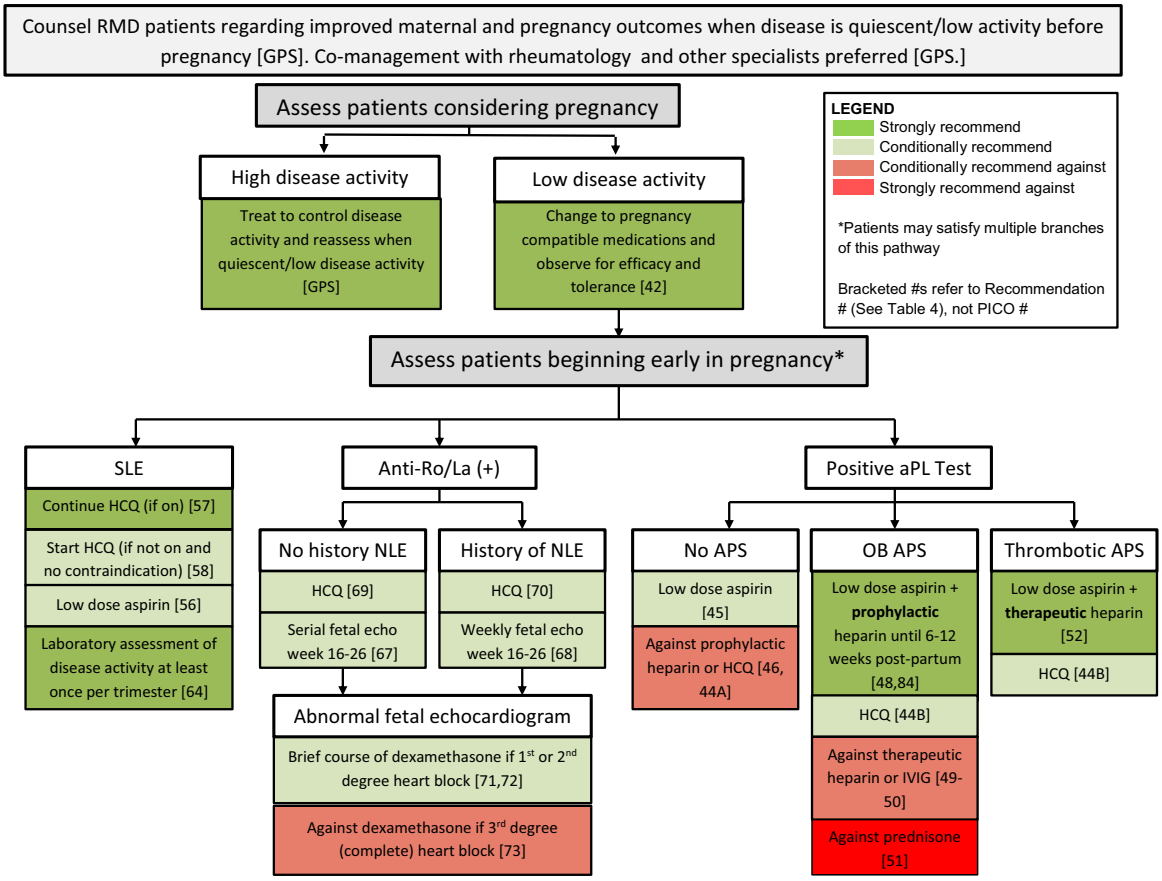
Counsel RMD patients regarding improved maternal and pregnancy outcomes when disease is quiescent/low activity before pregnancy [GPS]. Co-management with rheumatology and other specialists preferred [GPS.]
Assess patients considering pregnancy
High disease activity
Treat to control disease activity and reassess when quiescent/low disease activity [GPS]
Low disease activity
Change to pregnancy compatible medications and observe for efficacy and tolerance [42]
LEGEND
Strongly recommend
Conditionally recommend
Conditionally recommend against
Strongly recommend against
*Patients may satisfy multiple branches of this pathway
Bracketed #s refer to Recommendation # (See Table 4), not PICO #
Assess patients beginning early in pregnancy*
SLE
Continue HCQ (if on) [57]
Start HCQ (if not on and no contraindication) [58]
Low dose aspirin [56]
Laboratory assessment of disease activity at least once per trimester [64]
Anti-Ro/La (+)
No history NLE
HCQ [69]
Serial fetal echo week 16-26 [67]
History of NLE
HCQ [70]
Weekly fetal echo week 16-26 [68]
Abnormal fetal echocardiogram
Brief course of dexamethasone if 1st or 2nd degree heart block [71,72]
Against dexamethasone if 3rd degree (complete) heart block [73]
Positive aPL Test
No APS
Low dose aspirin [45]
Against prophylactic heparin or HCQ [46, 44A]
OB APS
Low dose aspirin + prophylactic heparin until 6-12 weeks post-partum [48,84]
HCQ [44B]
Against therapeutic heparin or IVIG [49-50]
Against prednisone [51]
Thrombotic APS
Low dose aspirin + therapeutic heparin [52]
HCQ [44B]

Figure 4. Recommendations and good practice statements (GPS) for pregnancy counseling, assessment, and management in women with rheumatic and musculoskeletal disease (RMD). SLE = systemic lupus erythematosus; HCQ = hydroxychloroquine; NLE = neonatal lupus erythematosus; aPL = antiphospholipid antibody (persistent moderate-to-high–titer anticardiolipin or anti–β_2-glycoprotein I antibody or persistent positive lupus anticoagulant); APS = antiphospholipid syndrome (obstetric and/or thrombotic); obstetric APS (OB APS) = patients meeting laboratory criteria for APS and having prior consistent pregnancy complications (≥3 consecutive losses prior to 10 weeks' gestation, fetal loss at or after 10 weeks' gestation, or delivery at <34 weeks due to preeclampsia, intrauterine growth restriction, or fetal distress) and with no history of thrombosis; thrombotic APS = patients meeting laboratory criteria for APS and having a prior thrombotic event (arterial or venous), regardless of whether they have had obstetric complications; IVIG = intravenous immunoglobulin; PICO = population, intervention, comparator, outcomes.

In women with RMD who are currently pregnant and have active disease that requires medical therapy, we strongly recommend initiating or continuing a pregnancy-compatible steroid-sparing medication, as both active RMD and continuous high-dose glucocorticoid treatment have potential for maternal and fetal harm (99).

Pre-pregnancy or early pregnancy laboratory testing for relevant autoantibodies is recommended. Ascertaining anti-Ro/SSA, anti-La/SSB, and aPL status improves counseling regarding pregnancy and fetal risk.

We strongly recommend testing for anti-Ro/SSA and anti-La/SSB once before or early in pregnancy in women with SLE or SLE-like disorders, Sjögren's syndrome, systemic sclerosis, and rheumatoid arthritis. Given the relative persistence and unchanged titers of these antibodies, we strongly recommend *against* repeating the test during pregnancy.

Patients with scleroderma renal crisis. Most disease-specific recommendations for RMD pregnancy management focus on presence of underlying SLE or positive aPL. One aspect of disease in systemic sclerosis, however, is of particular importance during pregnancy: the development of scleroderma renal crisis. While effective medications are usually contraindicated during pregnancy due to risk of adverse fetal effects, they should be considered in this unusual and life-threatening circumstance.

We strongly recommend use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockade therapy to treat active scleroderma renal crisis in pregnancy, because the risk of maternal or fetal death with untreated disease is higher than the risk associated with use of these medications during pregnancy.

While scleroderma renal crisis is rare in pregnancy (an estimated 2% of scleroderma pregnancies), it can easily be confused

with preeclampsia. Angiotensin-converting enzyme inhibitors can be renal-protective and life saving (100); however, they are contraindicated in the second and third trimesters of pregnancy because of potential oligohydramnios or permanent fetal renal damage (101), and should be considered only for active scleroderma renal crisis.

SLE patients. Supplementary Appendix 7, Table E (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations for SLE pregnancy management, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 11 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

In women with SLE who are considering pregnancy or are pregnant, we strongly recommend testing for LAC, aCL, and anti-β_2GPI antibodies once before or early in pregnancy, and *against* repeating these tests during pregnancy.

We recommend that all women with SLE take hydroxychloroquine (HCQ) during pregnancy if possible. If a patient is already taking HCQ, we strongly recommend continuing it during pregnancy; if she is not taking HCQ, we conditionally recommend starting it if there is no contraindication.

Many studies support maternal and pregnancy benefit of HCQ and low risk for mother and fetus (84,102–111). Potential contraindications include allergy, adverse side effects, or intolerance.

We conditionally recommend treating SLE patients with low-dose aspirin (81 or 100 mg daily), beginning in the first trimester.

The American College of Obstetricians and Gynecologists and US Protective Health Task Force recommend aspirin 81 mg daily as prophylaxis in all patients at high risk for preeclampsia (97,112–117). Treatment with low-dose aspirin during pregnancy to prevent or delay the onset of gestational hypertensive disease is recommended for those with SLE or APS because of their increased risk and may be considered for women with other RMD diagnoses depending on individual clinical risk factors. Some investigators have used doses of aspirin up to 150 mg daily, but both the American College of Obstetricians and Gynecologists and the U.S. Preventive Services Task Force note that there is a lack of appropriate comparative studies to show the superiority of doses >100 mg per day. Low-dose aspirin is not thought to complicate anesthesia or delivery (112); however, a decision regarding discontinuation prior to delivery should be made by the obstetrician-gynecologist and anesthesiologist according to the patient's specific clinical situation.

Because active disease affects maternal and pregnancy outcome, we strongly suggest, as good practice, monitoring SLE disease activity with clinical history, examination, and laboratory tests at least once per trimester.

Abnormalities in the complete blood cell count, differential cell count, urinalysis results and urinary protein:creatinine ratio, or anti-DNA, C3, or C4 levels may indicate possible SLE flare and/or preeclampsia despite absence of clinical symptoms. Frequency of laboratory monitoring and rheumatology follow-up may vary with an individual patient's clinical status and medications.

Antiphospholipid antibody–positive patients. Pregnancies in patients with positive aPL or APS present specific challenges and may require additional monitoring and therapy. Supplementary Appendix 7, Table F (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 11 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

Antiphospholipid antibody is a major risk factor for pregnancy loss and other adverse pregnancy outcomes, especially in SLE patients (118). Anti-β_2GPI, aCL, and LAC should all be tested. Among aPLs, LAC conveys the greatest risk for adverse pregnancy outcome in women with or without SLE: the RR for adverse pregnancy outcome with LAC was 12.15 (95% CI 2.92–50.54, $P = 0.0006$) in the PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in APL syndrome and SLE) study (118). Other independent risk factors in aPL-positive women were younger age, history of thrombosis, and SLE.

Antiphospholipid antibody–positive patients without thrombosis or obstetric complications. Asymptomatic aPL-positive patients (those without pregnancy complications or history of thrombosis) are not generally treated with prophylactic therapy to prevent pregnancy loss. However, presence of aPL regardless of clinical history is considered a risk factor for development of preeclampsia.

In pregnant women with positive aPL who do not meet criteria for obstetric or thrombotic APS, we conditionally recommend treating with prophylactic aspirin, 81 or 100 mg daily, during pregnancy as preeclampsia prophylaxis.

Treatment should begin early in pregnancy (before 16 weeks) and continue through delivery.

Patients with obstetric and thrombotic APS. Pregnancy increases the risk of thrombosis due to both hemostatic and anatomic factors. Patients who meet criteria for APS—whether obstetric or thrombotic—should receive therapy with heparin (usually LMWH) to improve pregnancy outcome and/or reduce risk of thrombosis.

We strongly recommend combined low-dose aspirin and prophylactic-dose heparin (usually LMWH) for patients meeting criteria for OB APS (119–126).

This is based on evidence of moderate strength.

In women with OB APS, we further strongly recommend treating with prophylactic-dose anticoagulation for 6–12 weeks post partum (127).

In pregnant women with thrombotic APS, we strongly recommend treating with low-dose aspirin and therapeutic-dose heparin (usually LMWH) throughout pregnancy and post partum.

We conditionally recommend *against* using the combination of prophylactic-dose heparin and low-dose aspirin therapy for patients with positive aPL who do not meet criteria for OB APS.

We appreciate and stress, however, that benefit in individual high-risk circumstances, such as triple-positive aPL or strongly positive LAC results, advanced maternal age, or IVF pregnancy, may outweigh risks of this therapy, and decisions should be made with discussion between physician and patient, weighing potential risks and benefits.

Other therapies for refractory OB APS. Despite improved outcomes with standard therapy with low-dose aspirin and prophylactic heparin/LMWH, additional treatments are needed for patients who do not respond to standard therapy. Intravenous immunoglobuin, low-dose prednisone, increased dose of heparin/LMWH, and HCQ have all been suggested as additional or alternative treatments.

We conditionally recommend *against* treatment with intravenous immunoglobulin or an increased LMWH dose, as these have not been demonstrably helpful in cases of pregnancy loss despite standard therapy with low-dose aspirin and prophylactic heparin or LMWH.

Prophylactic-dose heparin and aspirin therapy for OB APS improves likelihood of live birth, but not necessarily full-term birth. Pregnancy loss occurs, despite treatment, in 25% of OB APS pregnancies. There are no data demonstrating improved outcomes with a higher dose of heparin, and only anecdotal data support the use of intravenous immunoglobulin.

We strongly recommend *against* adding prednisone to prophylactic-dose heparin or LMWH and low-dose aspirin in patients in whom standard therapy has been unsuccessful, since there are no controlled studies demonstrating a benefit.

We acknowledge, however, that this recommendation is based on a lack of compelling data rather than data showing no clear benefit, and also that potential risk with this therapy is likely to be strongly affected by daily dosage, with higher doses imparting greater risk of side effects.

We conditionally recommend the addition of HCQ to prophylactic-dose heparin or LMWH and low-dose aspirin therapy for patients with primary APS.

Recent small studies of APS pregnancies suggest that HCQ may decrease complications (111).

In pregnant women with positive aPL who do not meet criteria for APS and do not have another indication for the drug (such as SLE), we conditionally recommend *against* treating with prophylactic HCQ.

As with any unproven treatment, this therapy may be considered in specific circumstances, depending on a patient's values and preferences and after a discussion about risks and benefits.

Anti-Ro/SSA and/or anti-La/SSB antibodies in pregnancy. Neonatal lupus erythematosus (NLE) describes several fetal and infant manifestations caused by or associated with maternal anti-Ro/SSA (commonly) and anti-La/SSB autoantibodies. While isolated anti-La/SSB rarely imposes risk, when combined with anti-Ro/SSA, La/SSB antibodies may increase fetal risk (128). Prospective studies of infants born to women with anti-Ro/SSA and/or anti-La/SSB antibodies show that ~10% develop an NLE rash, 20% transient cytopenias, and 30% mild transient transaminitis (estimates vary widely between reports). These complications are short-lived and spontaneously resolve as the child's maternal antibodies disappear (129).

Complete (third-degree) heart block (CHB) occurs in ~2% of pregnancies of women with anti-Ro/SSA and/or anti-La/SSB antibodies who have not had a prior infant with NLE, and in 13–18% of pregnancies of women with a prior infant who had either cutaneous or cardiac NLE (130). Low-titer antibodies are probably not associated with the same risk of CHB as higher titers (131). CHB rarely occurs after week 26. It is irreversible, and management transfers to pediatric cardiologists. Approximately 20% of children with CHB die in utero or in the first year of life; more than half will need a pacemaker (128).

Supplementary Appendix 7, Table G (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations regarding pregnancy in women with anti-Ro/SSA and/or anti-La/SSB antibodies, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 11 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

In pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies but no history of an infant with CHB or NLE, we conditionally recommend serial fetal echocardiography (less frequent than weekly; interval not determined) starting between 16 and 18 weeks and continuing

through week 26. For women with a prior infant with CHB or other NLE we conditionally recommend fetal echocardiography weekly, starting at week 16–18 and continuing through week 26.

Recommendations regarding monitoring for and treatment of CHB in women with anti-Ro/SSA and/or anti-La/SSB are all conditional. Given the rarity of CHB, large case series are not available; most studies are retrospective and not randomized. An argument against screening includes the risk of identification and treatment of artifacts that do not impact offspring health, thus exposing both fetus and mother to long-term side effects of dexamethasone; this risk must be balanced against the potentially devastating impact of CHB. All discussions should acknowledge the limited data and consider the patient's values and preferences.

We conditionally recommend treating all women who are positive for anti-Ro/SSA and/or anti-La/SSB antibodies with HCQ during pregnancy.

This is based on early and limited data and the low risk profile of HCQ. Retrospective studies demonstrate that in pregnant women with a prior child with cardiac NLE who take HCQ, there is a lower risk of the current fetus developing CHB (132).

For pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies and fetal first- or second-degree heart block shown on echocardiography, we conditionally recommend treatment with oral dexamethasone 4 mg daily. If CHB (without other cardiac inflammation) is present, we conditionally recommend *against* treating with dexamethasone.

Fluorinated glucocorticoids, such as dexamethasone and betamethasone, cross the placenta; low-to-moderate–dose nonfluorinated glucocorticoids, such as prednisone and prednisolone, are largely metabolized before they reach the fetus. Whether dexamethasone given for fetal first- or second-degree heart block changes outcome is a matter of controversy. Treatment should be limited to several weeks, depending on response, because of the risk of irreversible fetal and maternal toxicity. Whether dexamethasone improves long-term survival for a fetus with CHB is controversial (133,134), but recent analyses do not support its use (135).

Medication use

Paternal medication use. Supplementary Appendix 7, Table H (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents best practice statements and recommendations regarding paternal medication use in men with RMD, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 12 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Table 2 summarizes recommendations for paternal medication use.

Medication issues differ between men with RMD who are planning to father a pregnancy and those whose sexual partner is pregnant. Pre-conception, the concerns are potential effects on male fertility and medication-associated teratogenicity. There are few published data addressing these potential effects of medications for RMD. A decision to stop a medication must be weighed against the impact it may have on paternal disease activity.

When the man's partner is pregnant, the concern is whether his medication is present in seminal fluid and can transfer through vaginal mucosa, cross the placenta, and be teratogenic. In fact, post-conception exposure of the embryo or fetus is likely minimal,

Table 2. Recommendations regarding medication use for men with rheumatic and musculoskeletal disease who are planning to father a child

Strongly recommend continuing	Conditionally recommend continuing	Strongly recommend discontinuing	Conditionally recommend discontinuing	Unable to make a recommendation due to limited data
Azathioprine/ 6-mercaptopurine Colchicine Hydroxychloroquine Tumor necrosis factor inhibitors (all)	Anakinra Cyclooxygenase 2 inhibitors Cyclosporine Leflunomide Methotrexate Mycophenolate mofetil Mycophenolic acid Nonsteroidal anti-inflammatory drugs Rituximab Sulfasalazine *(semen analysis if delayed conception)* Tacrolimus	Cyclophosphamide *(discontinue 12 weeks prior to attempted conception)*	Thalidomide *(discontinue 4 weeks prior to attempted conception)*	Abatacept Apremilast Baricitinib Belimumab Secukinumab Tocilizumab Tofacitinib Ustekinumab

Table 3. Maternal medication use: overview of medication use before and during pregnancy, and during breastfeeding

Medication	Pre-conception	During pregnancy	Breastfeeding
Conventional medications			
Hydroxychloroquine	++	++	++
Sulfasalazine	++	++	++
Colchicine	++	++	++
Azathioprine, 6-mercaptopurine	++	++	+ Low transfer
Prednisone	+ Taper to <20 mg/day by adding pregnancy-compatible immunosuppressants	+ Taper to <20 mg/day by adding pregnancy-compatible immunosuppressants	+ After a dose of >20 mg, delay breastfeeding for 4 hours
Cyclosporine, tacrolimus	+ Monitor blood pressure	+ Monitor blood pressure	+ Low transfer
Nonsteroidal antiinflammatory drugs (cyclooxygenase 2 inhibitors not preferred)	+ Discontinue if the woman is having difficulty conceiving	+ Continue in first and second trimesters; discontinue in third trimester	+ Ibuprofen preferred
Tumor necrosis factor inhibitors (tumor necrosis factor inhibitors are considered compatible with pregnancy)			
Certolizumab	++	++	++
Infliximab, etanercept, adalimumab, golimumab	+ Continue through conception	+ Continue in first and second trimesters; discontinue in third trimester several half-lives prior to delivery	++
Rituximab	+ Discontinue at conception	+ Life-/organ-threatening disease	++
Other biologics (limited safety data; limited transfer in early pregnancy but high transfer in second half of pregnancy)			
Anakinra, belimumab, abatacept, tocilizumab, secukinumab, ustekinumab	+ Discontinue at conception	× Discontinue during pregnancy	+ Expect minimal transfer due to large molecular size, but no available data
Not compatible with pregnancy			
Methotrexate	×× Stop 1–3 months prior to conception	×× Stop and give folic acid 5 mg/day	× Limited data suggest low transfer
Leflunomide	×× Cholestyramine washout if detectable levels	×× Stop and give cholestyramine washout	××
Mycophenolate mofetil and mycophenolic acid	×× Stop >6 weeks prior to conception to assess disease stability	××	××
Cyclophosphamide	×× Stop 3 months prior to conception	+ Life-/organ-threatening disease in second and third trimesters	××
Thalidomide	×× Stop 1–3 months prior to conception	××	××
Tofacitinib, apremilast, baricitinib	Unable to determine due to lack of data; small molecular size suggests transfer across the placenta and into breast milk		

++ Strongly recommend

\+ Conditionally recommend

× Conditionally recommend against

×× Strongly recommend against

as seminal concentrations of medications and volumes transferred are small (136). There are no reports of post-conception teratogenesis attributable to medications taken by a man with RMD. When a man's sexual partner is pregnant, reassurance regarding low risk associated with his RMD treatment is generally warranted.

In the absence of adequate data regarding paternal exposure for most medications used for RMD, we developed recommendation statements when 1) at least some data on paternal exposure were available, 2) accumulated clinical experience of paternal exposure could guide the recommendation, or 3) there were no data on paternal exposure, but maternal exposure demonstrates teratogenicity. We do not present recommendations for new medications with no available class-level or drug-specific data.

We strongly recommend *against* use of CYC and thalidomide in men prior to attempting conception.

Paternal use of CYC may impair spermatogenesis or be mutagenic for DNA (137) and should be discontinued 3 months prior to attempting conception. Thalidomide is detectable in seminal fluid and is strongly teratogenic when given to pregnant women (138,139), and should be discontinued at least 1 month prior to attempting conception. The remaining medications are recommended either strongly or conditionally for continuation during peri- and post-conception periods.

In men with RMD who are planning to father a pregnancy, we strongly recommend continuation of HCQ, azathioprine, 6-mercaptopurine, colchicine, and tumor necrosis factor inhibitors (140–142).

In men with RMD who are planning to father a pregnancy, we conditionally recommend, based on a smaller body of evidence, continuing treatment with MTX, MMF, leflunomide, sulfasalazine, calcineurin inhibitors, and nonsteroidal antiinflammatory drugs (NSAIDs) (142–149).

Although the drug label suggests discontinuation of MTX before attempting pregnancy, data show no evidence for mutagenesis or teratogenicity (143–145).

Although sulfasalazine may affect sperm count and quality, there are no data suggesting teratogenicity (146,150), and we conditionally recommend its continuation. If conception does not occur, semen analysis should be considered.

We conditionally recommend continuation of anakinra and rituximab based on limited data (151,152).

Maternal medication use. Supplementary Appendix 7, Tables I (conventional rheumatology medications), J (biologic rheumatology medications), and K (glucocorticoids) (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) present formal best practice statements and recommendations regarding maternal medication use in patients with RMD, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 12 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Table 3 summarizes recommendations for maternal medication use.

As standard good practice, we suggest discussing medications well before the patient attempts to conceive; we also suggest discussing pregnancy plans prior to initiating treatment with medications that may affect gonadal function, such as CYC.

There are no published data regarding specific timing for medication discussion, which will vary according to the individual clinical situation, but in general we suggest adequate time to allow for appropriate medication changes and demonstration of tolerability and disease stability, usually a minimum of several months.

MTX, MMF, CYC, and thalidomide are known teratogens. We strongly recommend discontinuation of these within 3 months prior to conception (153–156).

Data regarding timing of discontinuation are conflicting and do not permit more specific recommendations. However, discontinuation within 1 menstrual cycle would represent the minimum, and 3 months the most common, period for discontinuation. In addition to concerns about teratogenicity, it is optimal to allow adequate time for observation of disease stability without medication.

For women treated with leflunomide, we strongly recommend cholestyramine washout if there are detectable serum levels of metabolite prior to or as soon as pregnancy is confirmed. Once metabolite is not detectable in the serum, the risks of pregnancy loss and birth defects are not elevated (157,158).

We conditionally recommend treatment with CYC for life-threatening conditions in the second or third trimester (86).

When potentially teratogenic medications are discontinued prior to pregnancy, we strongly recommend a period of observation without medication or transition to pregnancy-compatible medications to ensure disease stability (as discussed above). In women with inadvertent exposure to teratogenic medications we strongly suggest immediate referral to a maternal-fetal medicine specialist, pregnancy medication specialist, or genetics counselor as standard good practice.

We strongly recommend HCQ, azathioprine/6-mercaptopurine, colchicine, and sulfasalazine, medications commonly used for RMD, as compatible for use throughout pregnancy (104,106,159–161).

We conditionally recommend calcineurin inhibitors (tacrolimus and cyclosporine) and NSAIDs as compatible for use during pregnancy (154).

We conditionally recommend discontinuation of NSAIDs pre-conception if the patient is having difficulty conceiving (and if disease control would not be compromised), due to the possibility of NSAID-induced unruptured follicle syndrome, a cause of subfertility (162).

We strongly recommend *against* use of NSAIDs in the third trimester because of the risk of premature closure of the ductus arteriosus (163).

We conditionally recommend nonselective NSAIDs over cyclooxygenase 2–specific inhibitors in the first 2 trimesters, due to lack of data on cyclooxygenase 2–specific inhibitors.

Nonfluorinated glucocorticoids should be used when needed, but substitution of steroid-sparing pregnancy-compatible immunosuppressive therapy is desirable when high-dose or prolonged use is required.

We conditionally recommend continuing low-dose glucocorticoid treatment (≤10 mg daily of prednisone or nonfluorinated equivalent) during pregnancy if clinically indicated. We strongly recommend tapering higher doses of nonfluorinated glucocorticoids to <20 mg daily of prednisone, adding a pregnancy-compatible glucocorticoid-sparing agent if necessary. Although there are only minimal data regarding prolonged treatment with low-dose glucocorticoids during pregnancy, we conditionally recommend *against* routine administration of stress-dose glucocorticoids at the time of vaginal delivery, but conditionally do recommend such treatment for surgical (cesarean) delivery.

We conditionally recommend continuing tumor necrosis factor inhibitor therapy with infliximab, etanercept, adalimumab, or golimumab prior to and during pregnancy (164,165). The tumor necrosis factor inhibitor certolizumab does not contain an Fc chain and thus has minimal placental transfer (166). We strongly recommend continuation of certolizumab therapy prior to and during pregnancy.

Placental transfer and fetal exposure for most biologic therapies vary with gestational stage. The majority of RMD biologic therapies contain an Fc IgG1 construct that does not cross into the fetal circulation in significant concentrations until the second trimester (167). Use of the tumor necrosis factor (TNF) inhibitors that include an IgG1 Fc construct during the third trimester (infliximab, etanercept, adalimumab, and golimumab) results in high levels of placental transfer and significant drug levels in the neonate. A modest amount of evidence suggests that these TNF inhibitors cause no adverse effects, especially in the first trimester. There was extensive Voting Panel discussion regarding if, and when, these medications should be discontinued prior to delivery. The Voting Panel agreed that if the patient's disease is under good control, these medications may be discontinued in the third trimester. While there is a paucity of safety data, continuing TNF inhibitors through delivery if the patient's disease is active can be considered, with the understanding that the neonate will have significant serum levels of drug for a period of time.

There are limited data on the compatibility of other biologics with pregnancy. Given that these agents likely do not cross the placenta until the second trimester, the panel conditionally recommends that non–TNF inhibitor IgG-based molecules are compatible in the periconception period but should be discontinued during pregnancy (i.e. at the time of the first positive pregnancy test result).

We conditionally recommend continuing treatment with anakinra, belimumab, abatacept, tocilizumab, secukinumab, and ustekinumab while a woman is trying to conceive, but discontinuing once she is found to be pregnant.

If disease cannot be controlled with medications considered compatible with pregnancy, the physician and patient should discuss and weigh the possible risks from these medications versus the risks of uncontrolled disease during pregnancy.

We conditionally recommend continuing treatment with rituximab while a woman is trying to conceive, and we conditionally recommend continuing rituximab during pregnancy if severe life- or organ-threatening maternal disease so warrants.

Dosing in the second half of pregnancy puts the fetus at high risk of having minimal B cells at delivery (168).

There is no available evidence regarding use or safety of the new small-molecule agents, tofacitinib, baricitinib, and apremilast, during pregnancy. The Voting Panel elected not to offer recommendations regarding these drugs. It should be noted, however, that small molecules are likely to pass through the placenta.

Medication use during breastfeeding. The benefits of breastfeeding are numerous (169–175); the American Academy of Pediatrics recommends exclusive breastfeeding for the first 6 months and continued breastfeeding until 1 year (9). Because women with RMD may experience disease flare post partum and require treatment, it is important to balance benefits of disease control with risk of infant exposure through breast milk.

Infant serum levels of drugs ingested by the mother depend on multiple variables and are a function of drug concentration in breast milk, quantity of breast milk ingested, and drug absorption through the infant's gastrointestinal tract. Premature infants

Table 4. Reproductive health care in patients with RMD: concise recommendation summary*

Topic	Recommendation	Strength
Contraception		
All RMD	Contraception/pregnancy discussion early and regularly; choose contraception based on safety, efficacy, and patient preference	GPS
	Use barrier methods if unable to use other methods	GPS
	Use emergency contraception if necessary [6]	Strong
	Women receiving immunosuppressive medications: Use IUD if desired [7]	Strong
	Women at risk for osteoporosis: *Avoid* DMPA [10]	Conditional
	Women receiving MMF: Use IUD or 2 other methods together [11]	Conditional
	RMD without SLE or aPL: Use highly effective or effective methods† [1]	Strong
	Highly effective methods preferred to effective methods [1A]	Conditional
SLE	SLE with negative aPL and low/stable disease activity: Use highly effective or effective methods† [2]	Strong
	Highly effective methods preferred to effective methods [2A]	Conditional
	Avoid transdermal estrogen-progestin patch [2B]	Conditional
	SLE with negative aPL and moderate-to-high disease activity: Use progestin-only contraceptives or IUD [2C]	Strong
Positive aPL	Do *not* use combined estrogen-progestin contraceptives [3]; use IUD or progestin-only pill [4]	Strong
Assisted reproductive technology		
All RMD	Stable disease and negative aPL: Proceed with assisted reproductive technology:	
	IVF if pregnancy-compatible medications [24]	Strong
	Oocyte cryopreservation: Continue medications except CYC [28]	Strong
	Active disease: Defer assisted reproductive technology until disease is stable/quiescent [27]	Strong
SLE	Active SLE: Defer assisted reproductive technology until disease is stable/quiescent [27]	Strong
	Do *not* treat with prophylactic prednisone [29]	Conditional
Positive aPL	No prior thromboses or OB APS: Prophylactic heparin or LMWH [25A]	Conditional
	No prior thromboses but history of OB APS: Prophylactic heparin or LMWH [25A2]	Strong
	Prior thromboses: Therapeutic heparin or LMWH [26A]	Strong
Fertility preservation	Women: Use gonadotropin-releasing hormone agonist therapy during IV CYC treatment [31]	Conditional
	Men: Sperm cryopreservation pre–CYC treatment	GPS
	Do *not* use gonadotropin-releasing hormone agonist therapy [35]	Conditional
Menopause/hormone replacement therapy		
All RMD	RMD without SLE or aPL: Treat with hormone replacement therapy if indicated‡	GPS
SLE	SLE and negative aPL: Treat with hormone replacement therapy if indicated‡ [79]	Conditional
Positive aPL	If no prior thrombosis or OB APS: Do *not* treat with hormone replacement therapy [80]	Conditional
	If current titers negative, treat with hormone replacement therapy if indicated‡ [83]	Conditional
	If prior thrombosis or OB APS and not receiving anticoagulation treatment: Do *not* treat with hormone replacement therapy [81]	Strong
	If current titers negative, do *not* treat with hormone replacement therapy [83A]	Conditional
	If prior thrombosis or OB APS and receiving anticoagulation treatment: Do *not* treat with hormone replacement therapy [82]	Conditional
Pregnancy		
All RMD	Counseling: Outcomes improved with pregnancy planning, stable disease, compatible medications, and co-management by rheumatology and obstetrics-gynecology/maternal-fetal medicine	GPS
	Pre-pregnancy: Change to pregnancy-compatible medication and observe for stability [42]	Strong
	If active disease during pregnancy: Initiate pregnancy-compatible medication [54]	Strong
	If SLE or SLE-like disease, SS, SSc, or RA: Test once (early) for anti-Ro/SSA and anti-La/SSB [60, 62]	Strong
	If SSc and renal crisis during pregnancy: Treat with ACE inhibitor or ARB for life-threatening disease [55]	Strong

(Continued)

Table 4. (*Cont'd*)

Topic	Recommendation	Strength
SLE	SLE or SLE-like disease: Test once (early) for aPL (aCL, anti-β_2GPI, LAC) [59, 61]	Strong
	Continue HCQ during pregnancy [57]	Strong
	If not taking HCQ, start HCQ during pregnancy if no contraindications [58]	Conditional
	Monitor laboratory values at least once per trimester	GPS
	Treat with low-dose aspirin starting in first trimester [56]	Conditional
Positive aPL	Positive aPL only: If no prior thrombosis or OB APS, treat with low-dose aspirin starting in first trimester [45]	Conditional
	Do *not* treat with combination prophylactic heparin or LMWH/low-dose aspirin [46]	Conditional
	Do *not* treat with HCQ [44A]	Conditional
	OB APS: If no thrombosis but meet OB APS criteria, treat with combination prophylactic heparin or LMWH/low-dose aspirin [48]	Strong
	Do *not* treat with combination therapeutic heparin or LMWH/low-dose aspirin [49]	Conditional
	Do *not* treat with addition of IVIG [50]	Conditional
	Do *not* treat with addition of prednisone [51]	Strong
	Treat with addition of HCQ for combination heparin/low-dose aspirin failure [44B]	Conditional
	Treat with prophylactic anticoagulation during post partum period [84]	Strong
	Thrombotic APS: If prior thrombosis (meeting or not meeting OB APS criteria), treat with therapeutic heparin or LMWH/low-dose aspirin [52]	Strong
	Treat with addition of HCQ for therapeutic heparin or LMWH/low-dose aspirin therapy failure [44B]	Conditional
Positive anti-Ro/SSA with or without anti-La/SSB	Treat with HCQ during pregnancy [69, 70]	Conditional
	If no prior history of neonatal lupus: Serial (interval uncertain) fetal echocardiography in weeks 16–26 [67]	Conditional
	If prior history of neonatal lupus: Weekly fetal echocardiography in weeks 16–26 [68]	Conditional
	Abnormal fetal echocardiography: If first- or second-degree heart block, treat with dexamethasone 4 mg daily [71, 72]	Conditional
	If isolated third-degree heart block (and no other cardiac inflammation), do *not* treat with dexamethasone [73]	Conditional
Medication		
Paternal medication	If planning to father a child: Discuss medication use including CYC	GPS
	Discontinue CYC and thalidomide [133, 139]	Strong/conditional
	Continue HCQ, AZA, infliximab, etanercept, adalimumab, golimumab, certolizumab, colchicine [90, 115, 143, 146, 149, 152, 155, 97]	Strong
	Continue leflunomide, MMF, NSAIDs, sulfasalazine, cyclosporine, tacrolimus, anakinra, rituximab [108, 119, 85, 94, 126, 130, 159, 163]	Conditional
Maternal medication	If planning pregnancy: Discuss medication use including CYC	GPS
	If pregnant and exposed to teratogenic medications: Discontinue immediately, pursue counseling	GPS
	Discontinue NSAIDs if difficulty conceiving [86]	Conditional
	Avoid NSAIDs in third trimester [87]	Strong
	Use nonselective rather than COX-2–specific NSAIDs [88]	Conditional
	Discontinue MTX, MMF, thalidomide, CYC prior to conception [102, 120, 140, 134]	Strong
	Use CYC for life-threatening disease only in second and third trimester [136]	Conditional
	Discontinue leflunomide 24 months prior to conception or check serum metabolite levels and treat with cholestyramine washout [109, 110]	Strong
	Continue HCQ, sulfasalazine, AZA, colchicine [91, 95, 116, 98]	Strong
	Continue cyclosporine and tacrolimus [127, 131]	Conditional
	Continue certolizumab [156]	Strong
	Continue infliximab, etanercept, adalimumab, golimumab [144, 147, 150, 153]	Conditional
	Stop when pregnancy confirmed: rituximab, belimumab, anakinra, abatacept, tocilizumab, secukinumab, ustekinumab [164, 169, 160, 173, 177, 181, 185]	Conditional
	Use rituximab for organ- or life-threatening disease during pregnancy [165]	Conditional
	No recommendations for tofacitinib, baricitinib, apremilast due to lack of data [189, 193, 197]	
	Continue regular low-dose prednisone [201]	Conditional

(Continued)

Table 4. (*Cont'd*)

Topic	Recommendation	Strength
	Taper high-dose prednisone with addition of pregnancy-compatible drug if needed [202]	Strong
	Stress-dose steroid at delivery: do *not* treat for vaginal delivery, do treat for cesarean delivery [206, 207]	Conditional
Breastfeeding	Encourage breastfeeding and maintain disease control with compatible medications if possible	GPS
	Compatible medications:	
	HCQ, infliximab, etanercept, adalimumab, golimumab, certolizumab, rituximab [92, 143, 146, 149, 152, 155]	Strong
	NSAIDs, sulfasalazine, colchicine, AZA, cyclosporine, tacrolimus, anakinra, belimumab, abatacept, tocilizumab, secukinumab, ustekinumab [89, 96, 99, 117, 128, 132, 161, 170, 174, 178, 182, 186]	Conditional
	Prednisone or nonfluorinated steroid equivalent <20 mg daily [204]	Strong
	For prednisone ≥20 mg daily, discard breast milk obtained within 4 hours following medication [205]	Strong
	Do *not* treat with leflunomide, MMF, CYC, thalidomide [113, 124, 137, 142]	Strong
	Do *not* treat with MTX [106]	Conditional

* Recommendation numbers, shown in brackets, allow for cross-referencing with supplementary appendices. For more detailed/complete recommendations, see text or Supplementary Appendix 7 (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). RMD = rheumatic and musculoskeletal disease; GPS = good practice statement; MMF = mycophenolate mofetil (and mycophenolic acid); SLE = systemic lupus erythematosus; aPL = antiphospholipid antibody, meeting laboratory criteria for antiphospholipid syndrome (APS) (Supplementary Appendix 8, http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract); IVF = in vitro fertilization; CYC = cyclophosphamide; OB APS = APS meeting laboratory criteria and clinical obstetric criteria (Supplementary Appendix 8); LMWH = low molecular weight heparin; IV = intravenous; SS = Sjögren's syndrome; SSc = systemic sclerosis; RA = rheumatoid arthritis; ACE inhibitor = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; aCL = anticardiolipin antibody; anti-β_2GPI = anti–β_2-glycoprotein I; LAC = lupus anticoagulant; HCQ = hydroxychloroquine; IVIG = IV immunoglobulin; AZA = azathioprine (and 5-fluorouracil); NSAIDs = nonsteroidal antiinflammatory drugs; COX-2 = cyclooxygenase 2; MTX = methotrexate.
† Highly effective contraceptives are long-acting reversible contraceptives including progestin or copper intrauterine device (IUD) and progestin implant. Effective contraceptives are estrogen-progestin contraceptives (oral, patch, or vaginal ring) and progestin-only (oral, depot medroxyprogesterone acetate [DMPA]).
‡ General indication for hormone replacement therapy: Current recommendations suggest limiting hormone replacement therapy use in healthy postmenopausal women and using the lowest dose that alleviates symptoms for the minimum time necessary. Benefit-risk balance is most favorable for severe vasomotor symptoms in women ≤60 years old or within 10 years of menopause onset (ref. 61).

or those with gastrointestinal disorders may absorb medication differently. Rheumatologists should collaborate with pediatricians when making recommendations (176). Levels of drug in breast milk are routinely expressed as the relative infant dose (infant dose mg/kg/day divided by maternal dose mg/kg/day) and are available in reference publications; a value of <10% is considered safe.

Supplementary Appendix 7, Table L (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal best practice statements and recommendations for use of medications during breastfeeding, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 12 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

We suggest as standard good practice that women with RMD be encouraged to breastfeed if they so desire and are able to do so. In addition, we suggest that disease control be maintained with lactation-compatible medications and that individualized risks and benefits be reviewed with each patient.

Fortunately, many RMD medications may be initiated or continued during lactation.

We strongly recommend treatment with HCQ, colchicine, sulfasalazine, rituximab, and all TNF inhibitors as compatible with breastfeeding (177–181).

We also recommend prednisone <20 mg daily (or equivalent nonfluorinated glucocorticoid) as compatible with breastfeeding, but strongly recommend that with doses of prednisone ≥20 mg a day (or equivalent), women delay breastfeeding or discard breast milk accumulated in the 4 hours following glucocorticoid administration.

We conditionally recommend treatment with azathioprine/6-mercaptopurine, calcineurin inhibitors, NSAIDs and the non–TNF inhibitor biologic agents (anakinra, rituximab, belimumab, abatacept, tocilizumab, secukinumab, and ustekinumab) as compatible with breastfeeding (182–184).

We strongly recommend *against* use of CYC, leflunomide, MMF, and thalidomide while breastfeeding. We conditionally recommend *against* use of MTX while breastfeeding.

Despite minimal passage of MTX into breast milk, especially with once-weekly dosing, this medication may accumulate in neonatal tissues (185,186).

The Voting Panel declined to vote on the compatibility of new small-molecule agents regarding use during breastfeeding due to absence of data. In theory, however, these medications may transfer into breast milk because of their low molecular weights.

DISCUSSION

Patients' reproductive health concerns are relevant for all practicing rheumatologists. Issues regarding contraception, fertility, pregnancy, lactation, and the offspring's health affect almost every patient across all RMD diagnoses. The importance of this area is highlighted by recent publications that have addressed key elements of reproductive health for some or all RMD patients. The European League Against Rheumatism (EULAR) published recommendations regarding women's health issues in patients with SLE and APS (187), and both EULAR (with points to consider) and the British Society for Rheumatology/British Health Professionals in Rheumatology (with guideline recommendations) addressed use of medications before, during, and after RMD pregnancy (188–190). Here, we address broad reproductive health concerns as well as medication use surrounding pregnancy for all RMD patients, with special attention, when indicated, for patients with specific disorders such as SLE or APS.

Even with the wide spectrum of reproductive issues addressed here (Table 4), this project has important limitations. This guideline was developed, and the literature review conducted, in the adult population. An important future step will be to consider these issues among adolescents, as counseling and care for these patients may differ.

Another important limitation is the inability to include recommendations for uncommon but important clinical situations. Although our mandate was broad, our task was to derive and support our recommendations with available evidence, but many uncommon clinical scenarios have little published data. One such situation that reflects an ongoing research need is the challenge of reproductive health issues specific to transgender individuals, especially regarding hormonal therapies.

A relatively rare but important scenario is the therapeutic termination of pregnancy in patients with life-threatening disease damage or flare. Pregnancy in patients with preexisting severe organ damage carries profound maternal risk. Pulmonary arterial hypertension is associated with a particularly high risk of maternal mortality, estimated at up to 20% even with aggressive therapy (191). Other high-risk scenarios include severe renal insufficiency, cardiomyopathy, or valvular dysfunction. Severe autoimmune disease flare occurring during pregnancy—including diffuse alveolar hemorrhage, active nephritis or vasculitis, or central nervous system inflammation—also carries high risk for maternal morbidity and mortality (55,192–194). In these and other high-risk situations, the option of therapeutic termination of pregnancy may be lifesaving and should be discussed with the patient (195). Decisions regarding pregnancy termination in the setting of teratogenic medication exposure will depend on the specific medication, timing of exposure, and the patient's assessment of the available data; counseling by expert professionals such as maternal-fetal medicine or genetics specialists regarding degree of risk based on specific circumstances is suggested in these cases.

We provide data-derived recommendations for common clinical reproductive health decisions including recent advances in this area and emphasize the need for early involvement of the rheumatologist in reproductive health discussions involving patients with RMD, for instance, the importance of effective contraception. Almost half of pregnancies in the US are unplanned (196). In RMD patients unplanned pregnancies carry greater risk than do planned pregnancies in periods of low disease activity treated with compatible medications. Whether considering pregnancy or not, patients should know maternal and fetal risks, including fetal exposure to teratogenic medications and their safest and most effective contraception options.

Asking a patient about desire for pregnancy early and periodically (not only during perceived periods of change) and acknowledging her personal risk factors will ensure open dialog. New information supports a shift from the paradigm of discontinuing all RMD medications except prednisone, since pregnancy-compatible steroid-sparing disease-modifying antirheumatic drugs and biologic agents pose fewer short- and long-term risks to mother and infant. With adequate planning, treatment, and monitoring, most women with RMD can have successful pregnancies. Recent data indicate compatibility of many rheumatology medications both with lactation and with paternal use. The rheumatologist's familiarity with drug safety during these periods is important to maintain disease control and minimize mother and infant risk.

Fertility and postmenopausal issues are not uncommon in RMD patients. Recommendations regarding ART reflect a growing demand among patients with RMD for fertility therapies. Oocyte freezing is now widely available (197). Attention to disease activity and aPL status and discussion with reproductive endocrinology and infertility specialists will optimize safety. For patients undergoing CYC therapy, the greatest challenge is to consider preservation of gonadal function and to initiate protective treatment protocols. HRT is another issue of importance for postmenopausal RMD patients. Severe vasomotor symptoms may be debilitating and if affected patients do not have aPL, HRT may improve quality of life.

The strength of evidence on reproductive health topics in RMD patients is moderate at best, and usually low, very low, or nonexistent for many topics of interest. Identification of areas with weak evidence highlights research priorities. One need is to establish the long-term safety profile of highly effective contraceptives in RMD patients with and without aPL. Although low-dose aspirin for preeclampsia prophylaxis in SLE and aPL patients is a low-risk intervention, its effectiveness is not known. Management of OB APS is one area with moderately strong evidence, but treatment for women with recurring adverse

outcomes despite standard therapy is needed. Much in the field of prevention, screening, and management of NLE requires further study. There are very limited data on RMD medication effects on fertility and teratogenicity in men with RMD. Because women with RMD who plan to conceive, are pregnant, or are lactating are usually excluded from clinical trials, large-scale data about medication use in these populations are also lacking. Pregnancy registries collect these data but suffer reporting bias and may not reflect the racial and ethnic make-up of the patient population. Given the difficulties of collecting clinical data, research that focuses on better understanding of placental and breast physiology, as well as drug and antibody transport, may help inform decision-making.

With the development of this guideline, the ACR recognizes the key role of clinical rheumatologists not only in managing disease activity but also in understanding the interactions of RMDs and their therapies in the context of reproductive health. The most important goal of this guideline is to provide substance and direction for discussion between clinicians and patients. A second goal is to encourage development of close working relationships among rheumatologists, specialists in obstetrics-gynecology, maternal-fetal medicine, and reproductive endocrinology and infertility, and other involved clinicians. We present this guideline as a resource to share, discuss, and disseminate across specialties and patient groups.

ACKNOWLEDGMENTS

We thank Adegbenga Bankole, MD, Karen Costenbader, MD, MPH, and Michael Weisman, MD for serving on the Expert Panel. We thank Roger Levy, MD, PhD for participating in the initial guideline scoping meeting. We thank Liana Frankel, MD for leading the Patient Panel meeting, as well the patients who (along with authors Rachelle Crow-Hercher and C. Whitney White) participated in this meeting: Jenee Johnson, Kamanta Kettle, Nicole Lumpkin, Teona Osborne, Melissa Perry-Bell, Mera Ramkissoon, Zenethia Roberts, Kaci Jackson Sanderson, Paula Sosin, and Bene Williams. We thank the ACR staff, including Regina Parker for assistance in organizing the face-to-face Patient Panel and Voting Panel meetings and coordinating the administrative aspects of the project and Robin Lane for assistance in manuscript preparation. We thank Janet Waters for help in developing the literature search strategy and performing the literature search and updates, and Janet Joyce for peer-reviewing the literature search strategy.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Sammaritano had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Juvenile diseases

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ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 12, December 2017, pp 2271–2282
DOI 10.1002/art.40320
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2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and Their Major Subgroups

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

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This article is published simultaneously in the December 2017 issue of *Annals of the Rheumatic Diseases*.

The views expressed herein are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government, or the NHS, the National Institute for Health Research, or the Department of Health (UK).

Supported by the European League Against Rheumatism, the American College of Rheumatology, The Myositis Association, and in part by the NIH (Intramural Research Program and the National Institute of Environmental Health Sciences), the European Science Foundation for the Euromyositis Register, the Swedish Research Council (grant K2014-52X-14045-14-3), and the regional agreement on medical training and clinical research between the Stockholm County Council and the Karolinska Institutet. The project also received support (not financial support/funding) from different associations: the American Academy of Neurology, the Childhood Arthritis and Rheumatology Research Alliance (CARRA; CARRA Inc. is funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH), Friends of CARRA, the Arthritis Foundation, the European Neuromuscular Centre, the International Myositis Assessment and Clinical Studies Group, the Muscle Study Group, the Rheumatologic Dermatology Society, the Pediatric Rheumatology European Society network for juvenile dermatomysitis, and the Pediatric Rheumatology International Trials Organization. Drs. Chinoy and Cooper's work in myositis is supported in part by Arthritis Research UK (grant 18474) and the Medical Research Council (grant MR/N003322/1). Dr. Vencovsky's work in myositis is supported by the Ministry of Health, Czech Republic (Project for Conceptual Development of Research Organization grant 00023728).

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Objective. **To develop and validate new classification criteria for adult and juvenile idiopathic inflammatory myopathies (IIM) and their major subgroups.**

Methods. **Candidate variables were assembled from published criteria and expert opinion using consensus methodology. Data were collected from 47 rheumatology, dermatology, neurology, and pediatric clinics worldwide. Several statistical methods were utilized to derive the classification criteria.**

Results. **Based on data from 976 IIM patients (74% adults; 26% children) and 624 non-IIM patients with mimicking conditions (82% adults; 18% children), new criteria were derived. Each item is assigned a weighted score. The total score corresponds to a probability of having IIM. Subclassification is performed using a classification tree. A probability cutoff of 55%, corresponding to a score of 5.5 (6.7 with muscle biopsy) "probable IIM," had best sensitivity/specificity (87%/82% without biopsies, 93%/88% with biopsies) and is recommended as a minimum to classify a patient as having IIM. A probability of ≥90%, corresponding to a score of ≥7.5 (≥8.7 with muscle biopsy), corresponds to "definite IIM." A probability of <50%, corresponding to a score of <5.3 (<6.5 with muscle biopsy), rules out IIM, leaving a probability of ≥50–<55% as "possible IIM."**

Conclusion. **The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for IIM have been endorsed by international rheumatology, dermatology, neurology, and pediatric groups. They employ easily accessible and operationally defined elements, and have been partially validated. They allow classification of "definite," "probable," and "possible" IIM, in addition to the major subgroups of IIM, including juvenile IIM. They generally perform better than existing criteria.**

Introduction

Idiopathic inflammatory myopathies (IIMs), collectively known as myositis, are heterogeneous disorders characterized by muscle weakness and muscle inflammation (1). The most common subgroups in adults are dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM) (2), and in children, juvenile DM (JDM).

The International Myositis Assessment and Clinical Studies group (IMACS) has developed consensus on outcome measures and definitions of improvement to be used in clinical trials for myositis (3,4). A prerequisite for clinical trials and other clinical studies is the inclusion of well-defined patient groups. A wide variety of diagnostic or classification criteria for myositis are used (2,5–16), but are generally derived empirically and not validated. The criteria of Bohan and Peter (7,8) are most widely used, but have limitations. Because they do not clearly specify how to exclude other forms of myopathy, they may misclassify IBM patients as having PM (13,17–19), and muscular dystrophies with inflammation as myositis, and each criterion is not defined explicitly. New discoveries in the last decade, such as myositis-specific autoantibodies, that are associated with distinct clinical phenotypes (2,20–22), may provide opportunities to

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Dr. Singh has received consulting fees from Savient, Regeneron, Merz, Iroko, Bioiberica, Crealta/Horizon, Allergan, WebMD, UBM (less than $10,000 each), and Takeda (more than $10,000) and research grants from Takeda and Savient; he also serves as the principal investigator for an investigator-initiated study funded by Horizon Pharmaceuticals through a grant to DINORA, Inc., a 501 (c)(3) entity, and is a member of the executive committee of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 36 companies.

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Submitted for publication March 14, 2017; accepted in revised form July 26, 2017.

improve the precision of classification, but have not been tested adequately (11,23).

The aim of this project was to develop classification criteria for adult and juvenile IIM. The specific goal was to define the minimum essential, easily available clinical and laboratory features to 1) distinguish IIM from mimicking conditions with high sensitivity and specificity, and 2) distinguish the major subgroups of IIM.

Methods

Study design. The International Myositis Classification Criteria Project (IMCCP), an international collaboration with experts from adult and pediatric rheumatology, neurology, dermatology, epidemiology, and biostatistics, was established in 2004 and followed at our best the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) recommendations for development of classification criteria from that time or published soon thereafter (24,25). A steering committee and a larger working committee with experts in IIM were formed (see Supplementary Table 1 and Supplementary Appendix, available online on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40320/abstract).

Using the nominal group technique, experts in IIM from the steering committee and the working committee (26–29) designed the study and validation experiments, assembled and defined candidate criteria from published myositis criteria (2,5–16) and other characteristics of myositis, and determined and assembled the IIM subgroup diagnoses and comparator conditions that were studied. A pilot study to assess the practicality of capturing the items showed a fair agreement of data availability from IIM and non-IIM cases (Supplementary Table 2, http://onlinelibrary.wiley.com/doi/10.1002/art.40320/abstract). Input was obtained from myositis experts, by email to the IMACS network, and requesting comments on the items, to maximize face and content validity (24,25). The steering committee revised the list of variables based on the comments and further suggestions from the IMACS network, and 93 variables (Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.40320/abstract) were selected by the steering committee for study in cases and comparators. A glossary and definitions were developed according to an ACR glossary (30,31) (Supplementary Table 4, http://onlinelibrary.wiley.com/doi/10.1002/art.40320/abstract). Data were abstracted from patients' records and entered into a web-based database.

Inclusion criteria for cases and comparators were 1) diagnosis for at least 6 months prior to study inclusion; 2) physician certainty of diagnosis—either known IIM or, as comparators, known non-IIM cases where myositis was considered in the initial differential diagnosis; and 3) patients with the most recent and complete data were prioritized to acquire the most complete data in a consistent manner. A maximum of 40 cases and an equal number of comparators were collected from each center.

The study was approved by the ethics committees at each site.

Data analysis and candidate criteria selection. The association of each variable with the diagnosis (IIM, non-IIM) was assessed by odds ratios and tested with the Fisher's exact test. The treating physician diagnosis was considered the gold standard for analysis. Three classification techniques were explored: 1) a sum-of-items model in which a patient was classified as a case if the patient had a specified number of items from a set of item; 2) a probability-score model; and 3) a classification tree. The ensuing candidate criteria were examined with respect to statistical performance and clinical relevance. Due to the observed superior discriminating performance of the probability-score model, the other models were set aside.

Criteria development. The probability-score model summed score points associated with the signs and symptoms present. The score points were obtained as coefficients of a logistic regression model used to combine multiple variables for predicting IIM. The statistical significance of the resulting increase in the goodness-of-fit of the model was assessed using the Wald test. The improvement in predictive ability was measured by the increment in specificity and sensitivity and summarized by the area under the receiver operating characteristic curve (AUC).

Pediatric experts are using fewer muscle biopsies for classification of JDM in clinical practice than adult rheumatologists. Thus, a second model not including biopsy variables was developed. Assessment of statistical performance for each score/probability cutoff value provided the basis for a recommendation of a cutoff value for IIM classification by the steering committee. The proposed cutoffs were then defined as possible, probable, and definite IIM. To facilitate use of the new criteria, a web-based calculator for the probability-score model was developed.

The new classification criteria were compared with previous IIM criteria. Their statistical performance, and number of patients per IIM subdiagnosis classified as IIM by the different criteria sets, were calculated.

To distinguish subgroups of patients classified with IIM according to the new criteria, a classification tree was developed. The tree was based on the variables in the new classification criteria, statistical analyses as described in a separate methodology paper, and on expert opinion.

Validation. The new criteria were internally cross-validated. Samples of equal size to the original sample were drawn from the entire population at random with replacement, so-called "bootstrap" samples (32). The bootstrap sample represented the training sample, and the remaining subjects not contained in the bootstrap sample constituted the validation sample. The probability score was applied to each bootstrap training sample separately and then utilized to predict IIM in the validation sample. The procedure was repeated in over 200 bootstrap samples, and the average AUC was calculated.

The performance of the new criteria for IIM including the subgroups was tested for sensitivity in 2 independent cohorts, the Euromyositis Register (https://euromyositis.eu/) and the Juvenile Dermatomyositis Cohort Biomarker Study and Repository (JDRG) (UK and Ireland) (https://www.juveniledermatomyositis.org.uk/).

The program Stata V.13 (StataCorp) was used for data management and statistical analyses. The statistical program R (R Core Team [2014]. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/) was used for some analyses.

A report detailing the methodology will be submitted as a separate publication (manuscript submitted).

Results

Study population. Data from 976 IIM patients (74.5% adults; 25.5% children) (Table 1) were collected between 2008 and 2011 from 23 European, 17 North American, 1 South American, and 6 Asian sites, representing IIM subgroups of JDM (n = 248), PM (n = 245), DM (n = 239), IBM (n = 176), amyopathic DM (ADM) (n = 44), hypomyopathic DM (n = 12), immune-mediated necrotizing myopathy (IMNM) (n = 11), and juvenile PM (n = 1). A total of 624 comparators (81.6% adults; 18.4% children) (Table 1) representing a broad spectrum of conditions that can mimic IIM were included, comprising systemic inflammatory diseases (36.5%), muscle dystrophies (16.0%), drug-associated or toxin-associated myopathies (7.9%), motor neuron diseases/neuropathies (7.7%), metabolic myopathies (6.9%), myalgias (4.5%), dermatologic diseases (3.7%), endocrine myopathies (3.7%), infectious myopathies (4.5%), mitochondrial myopathies (2.4%), neuromuscular diseases (2.6%), other myopathies (1.9%), immune-mediated skin conditions (0.5%), as well as other diagnoses (1.3%) (see Supplementary Tables 5 and 6, available online on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40320/abstract).

Candidate criteria selection and criteria development. Based on statistical models, 16 variables from 6 categories best distinguished IIM cases from comparators (Table 2), and each variable was assigned a weight (score) based on its influence to discriminate IIM from non-IIM. A total score was computed by adding score points corresponding to each criterion being present. The score can be converted into a probability of IIM (Figures A and B), by:

$$\text{Probability of IIM without muscle biopsy} = 1/[1 + \text{exponential}\ (5.33\ -\ \text{score})]$$

$$\text{Probability of IIM including muscle biopsy} = 1/[1 + \text{exponential}\ (6.49\ -\ \text{score})]^{*}$$

or by using the online web calculator (www.imm.ki.se/biostatistics/calculators/iim). Sensitivity and specificity for varying probability cutoffs are shown in Figures 1C and D.

Cutpoints for classification. The best balance between sensitivity and specificity was found for a probability of 55–60% for the criteria not including muscle biopsy data, and 55–75% when including muscle biopsies, or a total aggregated score of score of ≥5.5 and ≤5.7 (≥6.7 and ≤7.6 if biopsy is available).

Table 1. Demographic data of the International Myositis Classification Criteria Project cohort*

	IIM (n = 976)	Comparators (n = 624)
Sex, no. (%)		
Female	652 (66.8)	369 (59.1)
Male	324 (33.2)	255 (40.9)
Adult onset disease, no. (%)†	727 (74.5)	509 (81.6)
Childhood onset disease, no. (%)†	249 (25.5)	115 (18.4)
Age at onset of symptoms, median (IQR) years	44.0 (14.7–57.0)	41.0 (20.0–56.0)
Age at diagnosis, median (IQR) years	45.5 (16.2–59.3)	45.0 (25.8–58.0)
Disease duration from time of first symptom, median (IQR) years‡	4.0 (2.0–8.0)	4.0 (1.0–9.0)
Disease duration from time of diagnosis, median (IQR) years§	3.0 (1.0–6.0)	1.8 (0.0–4.5)
Ethnicity, no. (%)		
Caucasian	611 (62.6)	360 (57.7)
Asian	177 (18.1)	156 (25.0)
Hispanic	51 (5.2)	25 (4.0)
African	40 (4.1)	28 (4.5)
Native American	18 (1.8)	4 (0.6)
Pacific Islander	3 (0.3)	1 (0.2)
Mixed	37 (3.8)	22 (3.5)
Unknown	54 (5.5)	32 (5.1)
Disease onset, no. (%)¶		
Acute (days to 2 weeks)	45 (4.6)	64 (10.3)
Subacute (>2 weeks to ≤2 months)	237 (24.3)	88 (14.1)
Insidious (>2 months to years)	648 (66.4)	444 (71.2)
NA	46 (4.7)	28 (4.5)

* IIM = idiopathic inflammatory myopathies; IQR = interquartile range; NA = information not available.
† Onset of first symptoms assumed to be related to the disease.
‡ Time from first symptom to last clinical evaluation.
§ Time from diagnosis to last clinical evaluation.
¶ Onset and progression of the first symptoms of the syndrome to the full disease presentation.

* Correction added 16 August 2018 after online publication: the algorithms used for manual calculation of the score that a patient will obtain using the described classification criteria have been reversed.

Table 2. The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies (IIMs)

When no better explanation for the symptoms and signs exists, these classification criteria can be used			
	Score points		
Variable	Without muscle biopsy	With muscle biopsy	Definition
Age of onset			
Age of onset of first symptom assumed to be related to the disease ≥18 years and <40 years	1.3	1.5	18 ≤ age (years) at onset of first symptom assumed to be related to the disease <40
Age of onset of first symptom assumed to be related to the disease ≥40 years	2.1	2.2	Age (years) at onset of first symptom assumed to be related to the disease ≥40
Muscle weakness			
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7	Weakness of proximal upper extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5	Weakness of proximal lower extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Neck flexors are relatively weaker than neck extensors	1.9	1.6	Muscle grades for neck flexors are relatively lower than neck extensors as defined by manual muscle testing or other objective strength testing
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2	Muscle grades for proximal muscles in the legs are relatively lower than distal muscles in the legs as defined by manual muscle testing or other objective strength testing
Skin manifestations			
Heliotrope rash	3.1	3.2	Purple, lilac-colored, or erythematous patches over the eyelids or in a periorbital distribution, often associated with periorbital edema
Gottron's papules	2.1	2.7	Erythematous to violaceous papules over the extensor surfaces of joints, which are sometimes scaly. May occur over the finger joints, elbows, knees, malleoli, and toes
Gottron's sign	3.3	3.7	Erythematous to violaceous macules over the extensor surfaces of joints, which are not palpable
Other clinical manifestations			
Dysphagia or esophageal dysmotility	0.7	0.6	Difficulty in swallowing or objective evidence of abnormal motility of the esophagus
Laboratory measurements			
Anti–Jo-1 (anti–histidyl–transfer RNA synthetase) autoantibody present	3.9	3.8	Autoantibody testing in serum performed with standardized and validated test, showing positive result
Elevated serum levels of creatine kinase (CK)* *or* lactate dehydrogenase (LDH)* *or* aspartate aminotransferase (ASAT/AST/SGOT)* *or* alanine aminotransferase (ALAT/ALT/SGPT)*	1.3	1.4	The most abnormal test values during the disease course (highest absolute level of enzyme) above the relevant upper limit of normal
Muscle biopsy features—presence of:			
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7	Muscle biopsy reveals endomysial mononuclear cells abutting the sarcolemma of otherwise healthy, non-necrotic muscle fibers, but there is no clear invasion of the muscle fibers
Perimysial and/or perivascular infiltration of mononuclear cells		1.2	Mononuclear cells are located in the perimysium and/or located around blood vessels (in either perimysial or endomysial vessels)
Perifascicular atrophy		1.9	Muscle biopsy reveals several rows of muscle fibers, which are smaller in the perifascicular region than fibers more centrally located
Rimmed vacuoles		3.1	Rimmed vacuoles are bluish by hematoxylin and eosin staining and reddish by modified Gomori trichrome stain

* Serum levels above the upper limit of normal.

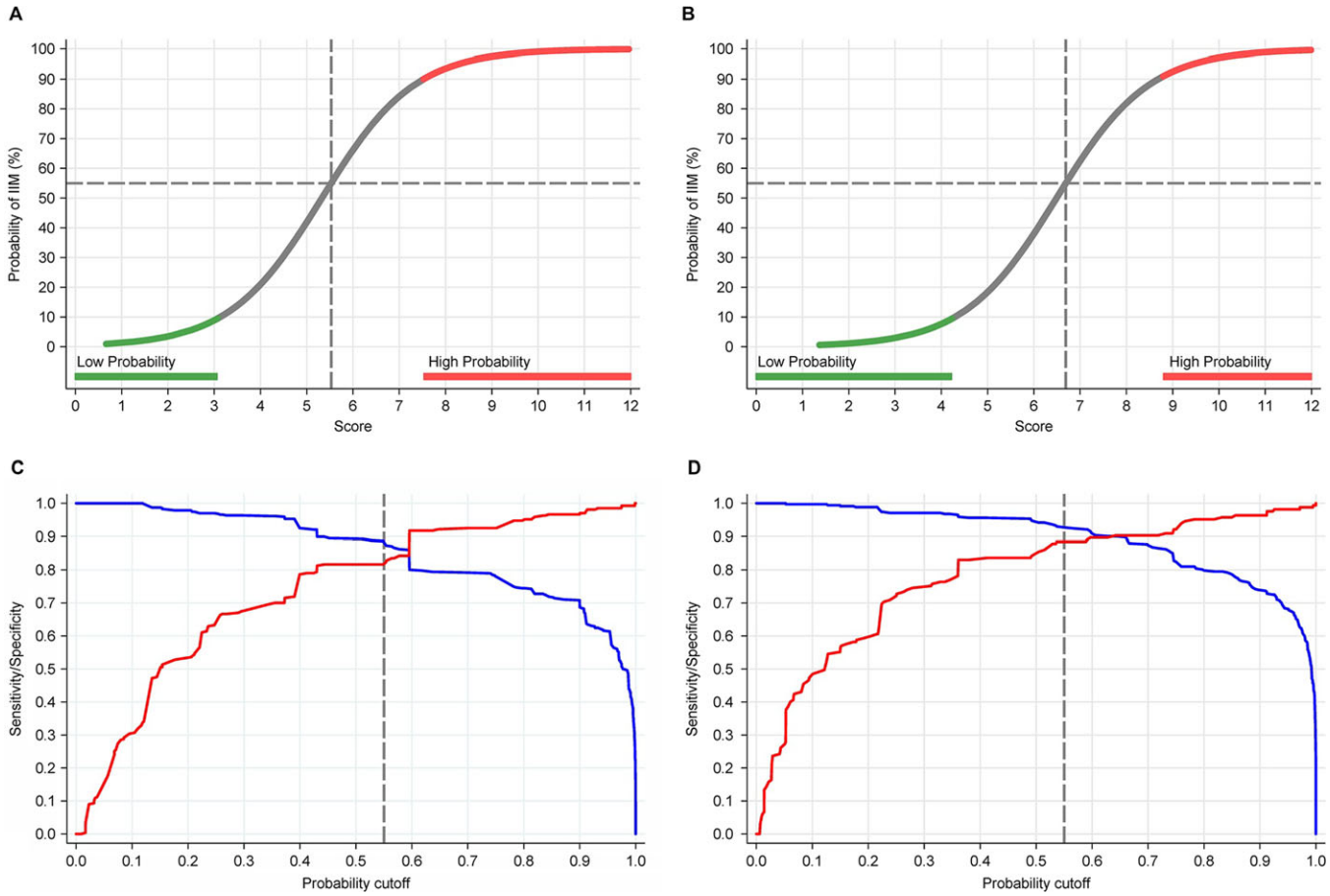

Figure 1. Probability of having idiopathic inflammatory myopathies (IIMs) based on the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for IIM. Each score obtained from the classification criteria corresponds to a probability of having the disease, without muscle biopsy data (**A**) or with muscle biopsy data (**B**). Each score and probability of disease display a unique set of sensitivity (blue line) and specificity (red line) measurements for the classification criteria not including muscle biopsy data (**C**) or including muscle biopsy data (**D**). The most optimal point of accuracy should be stated in publications and be appropriate to the intended purpose, with the recommendation of using a minimum of 55% probability (score of 5.5 without biopsies; 6.7 with biopsies) for classifying a case as IIM ("probable IIM") (dotted line). "Definite IIM" corresponds to a probability of at least 90% (score of ≥7.5 without biopsies; ≥8.7 with biopsies).

The IMCCP proposes that a patient may be classified as IIM if the probability exceeds a predetermined cutoff of at least 55% (corresponding to a score of ≥5.5, or ≥6.7 if biopsies are included) based on maximization of statistical performance and best balance between sensitivity and specificity. The level of probability ≥55% and <90% was defined as "probable IIM." The steering committee recommends, based on expert opinion, that "definite IIM" should equal a probability of ≥90%, corresponding to having total aggregate score of ≥7.5 without muscle biopsy and ≥8.7 with muscle biopsy.

Patients falling in the probability range ≥50% and <55% will be classified as "possible IIM." For a patient to be classified as a non-IIM patient, the probability would have to be <50% (score of <5.3 without biopsies; <6.5 with biopsies).

As suggested by pediatric experts and dermatologists, for patients with pathognomonic skin rashes of DM or JDM, classification criteria were developed, which did not include muscle biopsy data (Table 2). However, where no skin rash is present, a muscle biopsy is required for classification, as determined by a consensus of expert opinion within the IMCCP steering and working committees. Both sets apply equally well to adult IIM patients and to juvenile DM patients and should be used when IIM is suspected and no better explanation for the symptoms exists, as agreed on by expert opinion. Definitions for the criteria items are presented in Table 2.

Identification of subgroups. A patient classified with IIM by the EULAR/ACR classification criteria (probability of IIM ≥55%) can be further subclassified

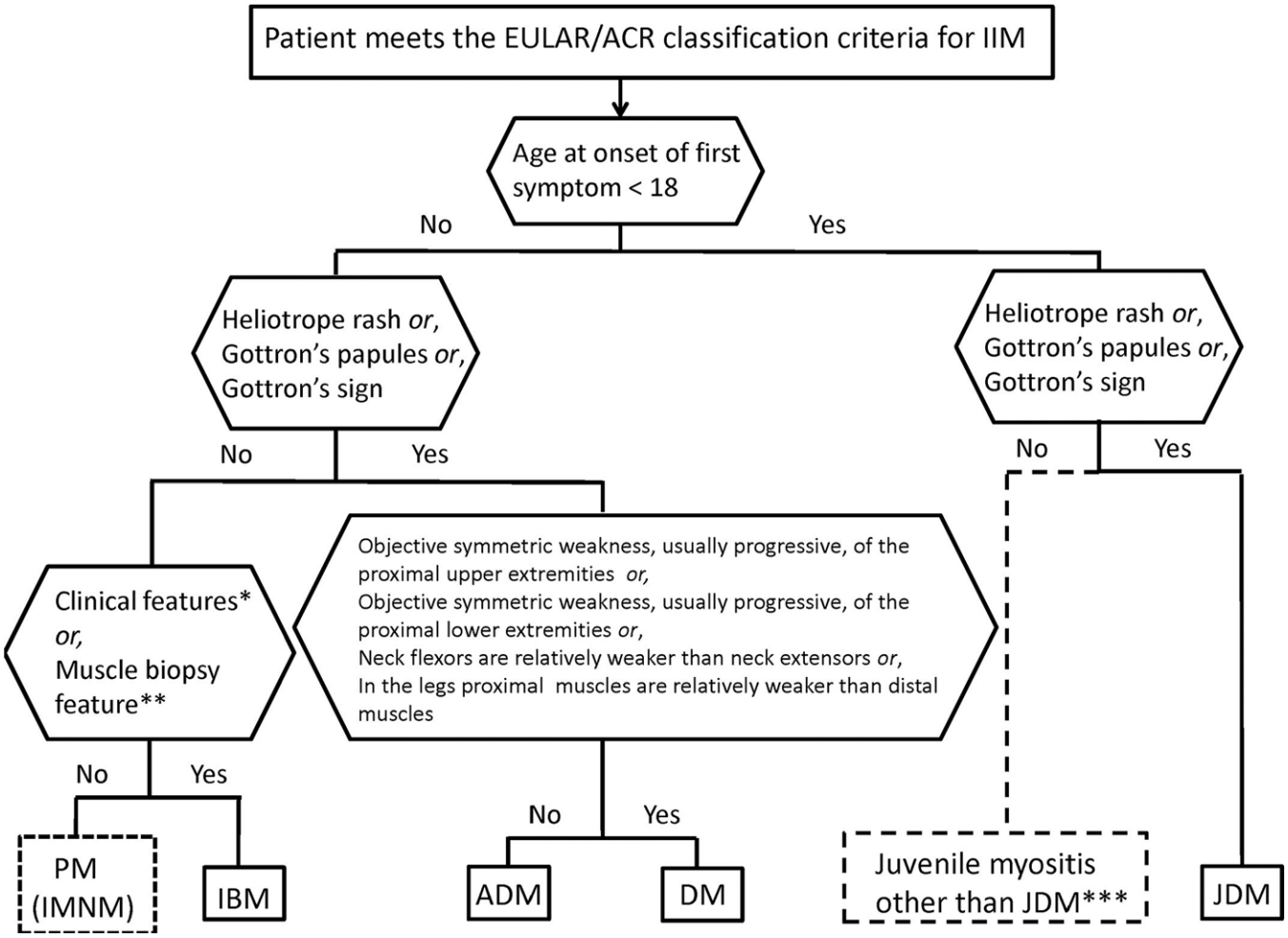
Patient meets the EULAR/ACR classification criteria for IIM
Age at onset of first symptom < 18
No
Yes
Heliotrope rash *or*, Gottron's papules *or*, Gottron's sign
Heliotrope rash *or*, Gottron's papules *or*, Gottron's sign
No
Yes
No
Yes
Clinical features* *or*, Muscle biopsy feature**
Objective symmetric weakness, usually progressive, of the proximal upper extremities *or*,
Objective symmetric weakness, usually progressive, of the proximal lower extremities *or*,
Neck flexors are relatively weaker than neck extensors *or*,
In the legs proximal muscles are relatively weaker than distal muscles
No
Yes
No
Yes
PM (IMNM)
IBM
ADM
DM
Juvenile myositis other than JDM***
JDM

Figure 2. Classification tree for subgroups of idiopathic inflammatory myopathies (IIMs). A patient must first meet the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for IIM (probability of IIM ≥55%). The patient can then be subclassified using the classification tree. The subgroup of polymyositis (PM) patients includes patients with immune-mediated necrotizing myopathy (IMNM). For inclusion body myositis (IBM) classification, one of the following is required for classification: finger flexor weakness and response to treatment: not improved (*), or muscle biopsy: rimmed vacuoles (**). *** = Juvenile myositis other than juvenile dermatomyositis (JDM) was developed based on expert opinion. IMNM and hypomyopathic dermatomyositis were too few to allow subclassification. ADM = amyopathic dermatomyositis; DM = dermatomyositis.

with a classification tree (Figure 2). Age at onset of first symptom (≥18 years of age) distinguishes adult from juvenile IIM. Thereafter, clinical findings and muscle biopsy features subclassify adult IIM patients into PM, IBM, ADM, or DM. Based on our data set, juvenile patients with skin rash can be classified into JDM. Three subgroups cannot be further separated using our criteria because of small sample sizes: juvenile PM, IMNM, and hypomyopathic DM.

Among patients with IIM by the EULAR/ACR classification criteria (probability of IIM ≥55%), and with sufficient data to allow subclassification (n = 703), the number of cases in the subgroups as defined according to the classification tree was enumerated (Table 3). The agreement between the classification tree subgroups and the physician-diagnosed subgroups in the data set was high (92.6% agreement; $\kappa = 0.90$, $P < 0.00001$). The agreement proportions, with a probability of 55%, were 1.00 for JDM, 0.89 for DM, 0.94 for ADM, 0.92 for IBM, and 0.93 for PM. Raising the probability cutoff of IIM to 90% yielded 94.9% agreement ($\kappa = 0.93$, $P < 0.00001$). With a probability cutoff of 90%, the agreement proportions were 1.00 for JDM, 0.96 for DM, 0.95 for ADM, 0.93 for IBM, and 0.88 for PM.

Performance of EULAR/ACR criteria compared with published criteria. Performance of the EULAR/ACR criteria was compared with published criteria for

Table 3. Comparison of physician-diagnosed idiopathic inflammatory myopathy (IIM) subgroups with IIM subgroups defined according to the classification tree among patients meeting the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for IIM*

	Classification tree subgroups†					
	JDM	DM	ADM	IBM	PM	Total
JDM	235	0	0	0	0	235
DM	0	191	6	2	15	214
ADM	1	1	30	0	0	32
IBM	0	0	0	66	5	71
PM	0	7	0	3	131	141
IMNM	0	0	0	0	10	10
Total	236	199	36	71	161	703
% of all IIM	33.6	28.3	5.1	10.1	22.9	–
% of adult IIM	–	42.6	7.7	15.2	34.5	–

* JDM = juvenile dermatomyositis; DM = dermatomyositis; ADM = amyopathic dermatomyositis; IBM = inclusion body myositis; PM = polymyositis; IMNM = immune-mediated necrotizing myopathy.
† Classification of IIM by the EULAR/ACR classification criteria for IIM, using a 55% probability cutofff for classification, followed by the classification tree for subclassification.

IIM (7,8,10,11,14,15) using the IMCCP data set (Table 4). The new criteria including muscle biopsy features displayed high sensitivity (93%) and specificity (88%). There was slightly lower performance without biopsy variables (sensitivity and specificity 87% and 82%, respectively). Among the assessed criteria, the Targoff criteria (11) showed the highest sensitivity (93%) and specificity (89%). Other criteria had either high sensitivity and low specificity (Bohan and Peter [7,8] and Tanimoto criteria [10]), or low sensitivity and high specificity (Dalakas and Hohlfeld [14] and European Neuromuscular Centre [ENMC] criteria [15]).

We studied how different criteria could classify patients with diverse IIM subdiagnoses in the IMCCP data set (Table 4). The EULAR/ACR classification criteria correctly classified most patients with all IIM subdiagnoses. When biopsy data were used, the performance improved for IBM (94% with biopsy data versus 58% without biopsy data) and PM (86% with biopsy data versus 79% without biopsy data). The Bohan and Peter (7,8), Tanimoto (10), and Targoff (11) criteria correctly classified all IIM subdiagnoses except ADM, a diagnosis not included in those criteria. The Dalakas and Hohlfeld criteria (14) could not classify any subdiagnoses. The ENMC criteria (15) correctly classified DM and JDM cases but no other subdiagnoses.

A comparison between the EULAR/ACR classification criteria (55% probability cutoff) and the Bohan and Peter criteria (7,8) showed 89% agreement ($\kappa = 0.71$, $P < 0.00001$) without including muscle biopsy data, and 93% agreement ($\kappa = 0.73$, $P < 0.00001$) using muscle biopsy findings. Comparison between the newly developed criteria and the Targoff criteria (11) demonstrated that the agreement was 89% ($\kappa = 0.74$, $P < 0.00001$) and 93% ($\kappa = 0.82$, $P < 0.00001$) without or with inclusion of muscle biopsy data, respectively.

Validation. *Internal validation.* Using the criteria without muscle biopsy data, 733 observations were used,

Table 4. Performance of the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for idiopathic inflammatory myopathies (IIMs) and existing classification and diagnostic criteria for IIM*

	The EULAR/ACR classification criteria for IIM†						
Performance	Without muscle biopsy	With muscle biopsy	Bohan and Peter (7,8)‡	Tanimoto et al (10)	Targoff et al (11)	Dalakas and Hohlfeld (14)‡	ENMC: Hoogendijk et al (15)‡
Sensitivity, mean (95% CI) %	87 (84–90)	93 (89–95)	98 (96–99)	96 (94–97)	93 (90–95)	6 (5–8)	52 (48–55)
Specificity, mean (95% CI) %	82 (77–87)	88 (83–93)	55 (50–61)	31 (25–37)	89 (84–92)	99 (98–100)	97 (95–98)
Positive predictive value, mean %	90	94	85	80	95	92	96
Negative predictive value, mean %	79	85	90	73	85	43	57
Correctly classified, mean %	86	91	86	79	91	45	70
Correct classification of IIM per subgroup, %§							
Amyopathic dermatomyositis	94	60	25	14	0	0	0
Dermatomyositis	96	98	100	96	99	7	83
Hypomyopathic dermatomyositis	83	100	80	40	67	0	20
Immune-mediated necrotizing myopathy	100	100	100	100	100	0	10
Inclusion body myositis	58	94	97	97	91	1	1
Juvenile dermatomyositis	97	96	100	96	98	5	86
Polymyositis	79	86	95	100	85	11	9

* ENMC = European Neuromuscular Centre; 95% CI = 95% confidence interval.
† Cutoff for probability: 55%.
‡ Definite and probable polymyositis and dermatomyositis.
§ Classification as idiopathic inflammatory myopathy per subgroup out of total number of cases per subgroup, expressed as the mean.

resulting in AUC = 0.942 and cross-validated area = 0.933. Using the criteria with muscle biopsy data, 507 observations were included, resulting in AUC = 0.962 and cross-validated area = 0.942.

External validation for sensitivity. Data from 592 cases (PM = 281, DM = 256, IBM = 33, JDM = 18, and ADM = 4) in the Euromyositis register were used where clinical, laboratory, and muscle biopsy data were available (Karolinska University Hospital, Stockholm, Sweden; Prague Hospital, Prague, Czech Republic; Oslo University Hospital, Oslo, Norway) (Supplementary Table 7, http://onlinelibrary.wiley.com/doi/10.1002/art.40320/abstract). When there was sufficient information available, the EULAR/ACR classification criteria confirmed IIM diagnosis using a 55% probability cutoff for classification of IIM with no misclassification, yielding 100% sensitivity. Using the criteria without muscle biopsies, 489 patients (83%) were classified as IIM, and 103 patients (17%) could not be classified due to missing data. For the criteria with biopsies, 204 (34%) were classified as IIM and 388 (66%) could not be classified due to missing muscle biopsy data in the register. Results for the IBM and PM subgroups improved when biopsy data were included: 97% of IBM cases could be classified, compared with 73% when biopsy data were not included. For PM, 80% and 76%, respectively, could be classified. Raising the IIM classification cutoff from 55% to 90% decreased the total number of cases that could be classified to only 63% (not including muscle biopsies) or 28% (including muscle biopsies) due to absence of some muscle biopsy variables in the Euromyositis registry database.

The Juvenile Dermatomyositis Biomarker Study and Repository (UK and Ireland). The JDRG register included 332 juvenile IIM cases in the study (definite JDM = 292, probable JDM = 20, definite juvenile PM = 4, probable juvenile PM = 2, focal myositis = 6, and other IIM = 8) (Supplementary Table 8, http://onlinelibrary.wiley.com/doi/10.1002/art.40320/abstract). Muscle biopsy data were not available for all; thus the EULAR/ACR classification criteria without muscle biopsy data were used to test sensitivity in this data set. Three hundred seven cases (92%) could be classified using the 55% cutoff and no case was misclassified, yielding 100% sensitivity. The remaining 25 cases (8%) could not be classified due to missing data. Raising the cutoff stepwise to 60%, 70%, 80%, or 90% yielded classification of 92%, 88%, 87%, or 64% cases, respectively, where classification was possible.

Web-calculator. A web-calculator was developed (www.imm.ki.se/biostatistics/calculators/iim) as an aid to use the EULAR/ACR classification criteria. A probability range of classification can be obtained, providing the minimum and maximum probability. In addition to the probabilities acquired, the aggregated scores will be displayed. Whenever sufficient data are entered, the subclassification will be displayed.

Discussion

Classification criteria are essential for inclusion of comparable patients in studies. No validated classification criteria for IIM currently exist. The EULAR/ACR classification criteria for IIM offer advantages that previous criteria lack. They are data-driven, exhibit high sensitivity and specificity, and use a limited number of accessible, defined clinical and laboratory variables. Internal validation and testing in external cohorts confirmed excellent performance. Importantly, the new criteria capture the most frequent IIM subgroups and can be used for both adults and children for research studies and clinical trials.

The new EULAR/ACR classification criteria provide a score with a corresponding probability of having IIM. This provides investigators flexibility in inclusion criteria for different types of studies, for example, clinical trials requiring high specificity would warrant a high probability of IIM in the inclusion criteria, whereas epidemiologic studies requiring high sensitivity would need inclusion criteria with lower probability of IIM.

The new criteria are based on data from children and adults with different ethnicities from centers in Europe, America, and Asia, and use symptoms, signs, and other measures that are routinely assessed. A limitation is still that a majority of the patients were Caucasian, and even though we included data from 298 patients from Asia, we cannot exclude that there can be differences in manifestations between different ethnic groups; hence we still need to validate the criteria in Asian and African populations. Importantly, in patients with a typical DM skin rash, the criteria can be used without muscle biopsy data. For JDM, 97% of patients were correctly classified using the new criteria without muscle biopsy data. The new criteria also offer practical advantages in the number of variables needed to be tested. If a sufficient probability is reached, there is no requirement to test all items. Each criterion is well-defined, lessening the opportunities for ad hoc interpretation. The skin rash typical of DM contributed with high weights in the probability score. Skin biopsy is recommended in the absence of muscle symptoms (33,34). The EULAR/ACR classification criteria are the first myositis criteria to be validated and tested for sensitivity in other cohorts and revealed no misclassification.

Compared with most previous criteria, the new criteria are superior in sensitivity, specificity, and classifi-

cation accuracy. Classification criteria should have high sensitivity and specificity. The EULAR/ACR criteria demonstrated sensitivity and specificity of 87% and 82%, respectively, with even higher accuracy when muscle biopsies were included: 93% and 88%, respectively. Correctly classified patients were 86% and 91%, respectively, with and without inclusion of biopsies, and the criteria performed equally well for adult and juvenile cases. The Targoff criteria (11) also showed good statistical properties, but were not able to capture all subgroups of IIM as ADM patients were not included. Furthermore, the variables were not clearly defined in the Targoff criteria, and testing of more variables is required, including electromyography, which is not always easily accessible and may be painful for patients. Importantly, the EULAR/ACR criteria can be applied to myositis patients with overlap diagnoses, such as mixed connective tissue disease or systemic lupus erythematosus with myositis, since these patients were included among IIM cases.

There are limitations of the study; no controls or comparators were included in the external validation cohort, since the IMCCP study was designed before those recommendations from ACR/EULAR were in place, requiring future validation. A validation study using comparators is underway, but we encourage additional validation studies in different populations. Another limitation largely unavoidable in observational data is the high frequency of missing data in the derivation data set and validation samples, reflecting differences in practice patterns in evaluating patients. Nevertheless, 80% of cases and comparators had muscle biopsy data available, whereas magnetic resonance imaging (MRI) data and electromyography were only available for 38% and 29% of cases, respectively, reflecting their limited usage in clinical diagnosis. However, MRI data and electromyography examination are still important for diagnostic purposes of IIM. Patients studied had to have their disease for at least 6 months, which did not allow us to study new-onset patients. Importantly, these criteria are proposed as classification criteria in research and in clinical trials, not as diagnostic criteria (35).There is also some possibility that the cut points established for probable and definite myositis will need adjustment when tested with new populations of patients.

It took almost 10 years to assemble sufficient numbers of patients with these rare diseases, and 3 subgroups did not have enough subjects to study adequately. During this period, a new IIM subgroup became recognized, IMNM (36), of which only a few cases were included in the study. IMNM cases could thus not be distinguished from PM in the subclassification tree. Another subgroup with few cases was juvenile PM, making a data-derived distinction from JDM impossible. However, pediatric rheumatology experts in the IMCCP recommended that the adult subclassification of IIM could be used for juvenile PM by extrapolation (Figure 2). IBM cases were identified in the subclassification tree by the clinical features of finger flexor weakness and no response to treatment, or by the presence of rimmed vacuoles in muscle biopsies (37).

Another limitation was the low frequency of myositis-specific autoantibodies documented. Five myositis-specific autoantibodies were included: anti–Jo-1, anti–Mi-2, anti–signal recognition particle, anti–PL-7, and anti–PL-12 antibodies, and all were strongly associated with IIM. However, only anti–Jo-1 autoantibody had a significant number of observations (n = 1,062) to permit analyses and inclusion in the classification criteria. A future update of the EULAR/ACR classification criteria should include the more recently-identified myositis-specific autoantibodies (21,22), in addition to more patients with IMNM, ADM, hypomyopathic DM, and juvenile cases other than JDM.

Recommendations

- Patients with pathognomonic skin rashes (heliotrope rash, Gottron's papules, and/or Gottron's sign) of JDM or DM are accurately classified with the EULAR/ACR classification criteria without including muscle biopsy data. For patients without these skin manifestations, muscle biopsy is recommended. For DM patients without muscle involvement, a skin biopsy is recommended.
- The EULAR/ACR classification criteria provide a score and a corresponding probability of having IIM. Each probability displays a unique sensitivity and specificity. The best balance between sensitivity and specificity can be found for a probability of 55–60% (total aggregated score of ≥5.5 and ≤5.7) for the criteria not including muscle biopsy data, and 55–75% (total aggregated score ≥6.7 and ≤7.6) when including muscle biopsies. These cases are designated "probable IIM." The recommended cutoff needed for classifying a patient as having IIM is ≥55%.
- "Definite IIM" corresponds to a probability of ≥90% or a total aggregate score of 7.5 or more without muscle biopsy and 8.7 with muscle biopsy, and is recommended in studies where a high specificity is required.
- A patient is termed "possible IIM" if the probability is ≥50% and <55% (a minimum score of 5.3 without biopsies and 6.5 with biopsies).
- For clarity and transparency, both the descriptive term ("possible," "probable," or "definite") and the probability and the aggregated score should be reported in studies.

Conclusions

New classification criteria for IIM and the major IIM subgroups have been developed. These data-driven criteria have a good feasibility, high sensitivity and specificity, have been partly validated in external cohorts, and are superior to previous criteria in capturing different subgroups of IIM. Revision of the criteria in the future will be important when additional validated myositis autoantibody tests, imaging, and other tests are available in more IIM cases and comparator cases without IIM.

ACKNOWLEDGMENTS

We thank Elin Forslund for assistance with data registration. We thank Dr. Andrew Mammen and Dr. Mike Ward for critical reading of the manuscript. We are grateful for contribution of clinical data from investigators and for participants contributing with valuable input at IMCCP meetings.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Lundberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lundberg, Tjärnlund, Bottai, Werth, Pilkington, de Visser, Alfredsson, Amato, Barohn, Liang, Singh, Dankó, Feldman, Kohsaka, Lachenbruch, Lang, Miller, Rider.

Acquisition of data. Lundberg, Tjärnlund, Bottai, Werth, Pilkington, de Visser, Alfredsson, Amato, Barohn, Liang, Singh, Aggarwal, Arnardottir, Chinoy, Cooper, Dankó, Dimachkie, Feldman, Garcia-De La Torre, Gordon, Hayashi, Katz, Kohsaka, Lachenbruch, Lang, Li, Oddis, Olesinska, Reed, Rutkowska-Sak, Sanner, Selva-O'Callaghan, Song, Vencovsky, Ytterberg, Miller, Rider, International Myositis Criteria Consortium working committee members.

Analysis and interpretation of data. Lundberg, Tjärnlund, Bottai, Werth, Pilkington, de Visser, Alfredsson, Amato, Barohn, Liang, Singh, Aggarwal, Feldman, Garcia-De La Torre, Gordon, Kohsaka, Lachenbruch, Lang, Li, Miller, Rider.

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Arthritis Care & Research
Vol. 71, No. 5, May 2019, pp 579–590
DOI 10.1002/acr.23834
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American College of Rheumatology Provisional Criteria for Clinically Relevant Improvement in Children and Adolescents With Childhood-Onset Systemic Lupus Erythematosus

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Objective. To develop a Childhood Lupus Improvement Index (CHILI) as a tool to measure response to therapy in childhood-onset systemic lupus erythematosus (cSLE), with a focus on clinically relevant improvement (CRI_{cSLE}).

Methods. Pediatric nephrology and rheumatology subspecialists (n = 213) experienced in cSLE management were invited to define CRI_{cSLE} and rate a total of 433 unique patient profiles for the presence/absence of CRI_{cSLE}. Patient profiles included the following cSLE core response variables (CRVs): global assessment of patient well-being (patient-global), physician assessment of cSLE activity (MD-global), disease activity index score (here, we used the Systemic Lupus Erythematosus Disease Activity Index), urine protein-to-creatinine ratio, and Child Health Questionnaire physical summary score. Percentage and absolute changes in these cSLE-CRVs (baseline versus follow-up) were considered in order to develop candidate algorithms and validate their performance (sensitivity, specificity, area under the receiver operating characteristic curve [AUC]; range 0–1).

Results. During an international consensus conference, unanimous agreement on a definition of CRI_{cSLE} was achieved; cSLE experts (n = 13) concurred (100%) that the preferred CHILI algorithm considers absolute changes in the cSLE-CRVs. After transformation to a range of 0–100, a CHILI score of ≥54 had outstanding accuracy for identifying CRI_{cSLE} (AUC 0.93, sensitivity 81.1%, and specificity 84.2%). CHILI scores also reflect minor, moderate, and major improvement for values exceeding 15, 68, and 92, respectively (all AUC ≥0.92, sensitivity ≥93.1%, and specificity ≥73.4%).

Conclusion. The CHILI is a new, seemingly highly accurate index for measuring CRI in cSLE over time. This index is useful to categorize the degree of response to therapy in children and adolescents with cSLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex, chronic, multisystem autoimmune inflammatory disease, with up to 20% of patients diagnosed during childhood (cSLE) (1,2). When lupus disease commences early in life rather than during adulthood, the prognosis is poorer, particularly due to multiorgan and kidney involvement (3,4). The course of cSLE is characterized by

Supported by the NIH (grants 5U01-AR-51868, P30-AR-AR47363, and 2UL1-RR-026314). Dr. Silva's work was supported by grants from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP 215/03756-4), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 303422/2015-7 and CNPq 304255/2015-7), and by Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente" da USP (NAP-CriAd). Dr. Ardoin's work was supported by CNPq 7/2016-9.

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SIGNIFICANCE & INNOVATIONS

- International consensus regarding a definition of clinically relevant improvement in children and adolescents with lupus has been achieved.
- The Pediatric Rheumatology International Trials Organization/American College of Rheumatology (ACR) provisional criteria for response to therapy in children with lupus have only fair accuracy for capturing clinically relevant improvement in children with lupus, as judged by physicians.
- Using strategies for the development of response measures in line with those suggested by the ACR, we newly developed and initially validated highly accurate criteria to measure clinically relevant improvement in children and adolescents with lupus.

episodes of disease flares followed by periods of improvement, generally due to more intensive drug therapy. There is international consensus that core response variables (cSLE-CRVs) should be considered when assessing response to therapy and cSLE disease flare (5,6). Considering changes in cSLE-CRVs, a provisional American College of Rheumatology (ACR) cSLE flare score can be calculated to identify patients who experienced a minor, moderate, or severe flare of cSLE (7,8). Likewise, percentage changes in cSLE-CRVs are the basis for the Pediatric Rheumatology International Trials Organization (PRINTO)/ACR provisional criteria for response to therapy (9).

We have previously shown, albeit in a rather small data set, that the PRINTO/ACR provisional criteria for response to therapy and, to a lesser extent, the Systemic Lupus Erythematosus Responder Index (SRI) are both very well suited to capture major improvement in cSLE; however, both the PRINTO/ACR provisional criteria for response to therapy and the SRI appeared less apt to identify patients who experienced moderate or minor improvement of cSLE (10). At present, there are no generally accepted criteria or algorithms to measure various degrees of improvement in cSLE, and consensus is lacking regarding what constitutes clinically relevant improvement (CRI_{cSLE}) in children and adolescents with cSLE. The latter is especially relevant, because in studies of rheumatoid arthritis, an ACR 20% improvement (ACR20) response, or in juvenile idiopathic arthritis (JIA) an ACR30 response (JIA-ACR30), provides such a measure of clinically relevant improvement. ACR20 and JIA-ACR30 responses, respectively, are regarded as improvement thresholds that can support labeling of new medications by the US Food and Drug Administration or the European Medicines Agency (11,12). Prior to developing criteria or algorithms to measure $CRI_{cSLE,}$ it is necessary to achieve consensus around a definition of CRI_{cSLE}.

Building on prior international consensus around the cSLE-CRVs that are needed to capture response to therapy in cSLE (9), the objectives of this study were to define CRI_{cSLE} and to develop, as well as initially validate, criteria to measure CRI_{cSLE}. Further, we sought to measure minor, moderate, and major responses to therapy in cSLE.

PATIENTS AND METHODS

The overall approach to this project was based on the methodologic framework successfully employed in pediatric rheumatology criteria development in the past (9,13,14), which is aligned with recommendations of the ACR Criteria Subcommittee and the Quality of Care Committee (15). As shown in Figure 1, an initial Delphi survey was conducted among 114 pediatric rheumatologists and nephrologists with expertise in cSLE (1) to delineate key features for judging whether a patient experienced CRI_{cSLE} (step 1). Subsequently, participants in a consensus conference rated 200 patient profiles (step 2). During a consensus conference, the results of steps 1 and 2 were reviewed to support consensus formation around a definition of CRI_{cSLE} (step 3)**.** This was followed by a second round of patient profiles sent to 200 pediatric rheumatologists and the cSLE experts who participated in the consensus conference. The resulting data set was randomly split into a training data set and a validation data set (step 4). The training data set was used to develop candidate criteria for CRI_{cSLE} (step 5). These candidate criteria were tested using the validation data set (step 6). As in step 3, agreement was achieved around a

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Dr. Brunner has received consulting fees from AbbVie, Ablynx, Amgen, AstraZeneca, Baxalta Biosimilars, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, EMD Serono, Gilead Sciences, Janssen, MedImmune, Novartis, Pfizer, R-Pharm, Roche, Servier, Takeda (less than $10,000 each), speaking fees from Genentech and Novartis (more than $10,000 each), and Scientific grant support from Pfizer and Bristol-Myers Squibb for research studies in adult lupus and juvenile idiopathic arthritis. Dr. Brunner is a full-time employee of Cincinnati Children's Hospital, which has received contributions from Bristol-Myers Squibb, Hoffman-La Roche, Janssen, Novartis, and Pfizer for the coordination activity of the Pediatric Rheumatology Collaborative Study Group network. Dr. Ravelli has received consulting and/or speaking fees from AbbVie, Bristol-Myers Squibb, Pfizer, Hoffman-LaRoche, Novartis, Centocor, "Francesco Angelini," and Reckitt Benckiser (less than $10,000 each). Dr. Avcin has received consulting and/or speaking fees from AbbVie and Boehringer Ingelheim (less than $10,000 each). Dr. Ruperto has received consulting and/or speaking fees from Abbott, AbbVie, Amgen, Biogenidec, Astellas, Alter, AstraZeneca, Baxalta Biosimilars, Boehringer, Bristol-Myers Squibb, CD Pharma, Celgene, Crescendo Bioscience, EMD Serono, Hoffman-La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, Novo Nordisk, Pfizer, R/Pharma, Sanofi Aventis, Servier, Sinergie, Takeda, Vertex, UCB Biosciences (less than 10,000 each). IRCCS Istituto Giannina Gaslini, the public hospital where Dr. Ruperto is a full-time public employee, has received contributions from Abbott, Bristol-Myers Squibb, "Francesco Angelini," GlaxoSmithKline, Hoffman-La Roche, Italfarmaco, Janssen, Novartis, Pfizer, Sanofi-Aventis, Schwarz Biosciences, Sobi, Xoma, and Wyeth (more than $10,000 each). No other disclosures relevant to this article were reported.

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Submitted for publication May 24, 2018; accepted in revised form January 8, 2019.

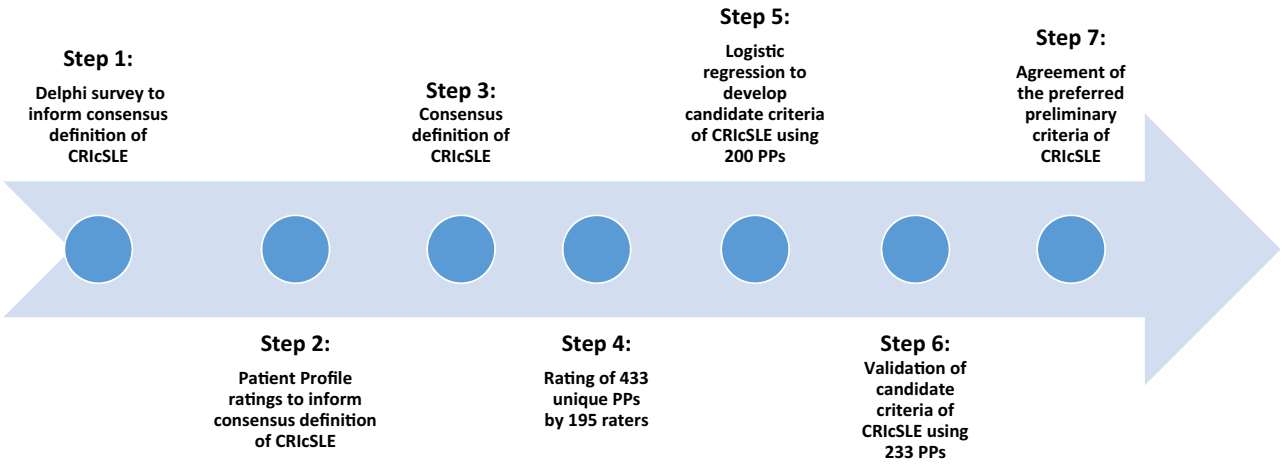
Step 1:
Delphi survey to inform consensus definition of CRIcSLE
Step 2:
Patient Profile ratings to inform consensus definition of CRIcSLE
Step 3:
Consensus definition of CRIcSLE
Step 4:
Rating of 433 unique PPs by 195 raters
Step 5:
Logistic regression to develop candidate criteria of CRIcSLE using 200 PPs
Step 6:
Validation of candidate criteria of CRIcSLE using 233 PPs
Step 7:
Agreement of the preferred preliminary criteria of CRIcSLE

Figure 1. Process of developing the criteria for clinically relevant improvement of childhood-onset systemic lupus erythematosus (cSLE). Consensus formation methodology was used, starting with a Delphi survey, a series of online ratings of patient profiles (PPs) by physicians experienced in the care of children with cSLE, a consensus conference, and final consensus about preferred criteria to measure clinically relevant improvement of cSLE (CRI_{cSLE}).

preferred Childhood Lupus Improvement Index (CHILI) algorithm among cSLE experts with voting rights who had participated in the consensus conference (step 7). See Appendix A for a list of the members of the Pediatric Rheumatology Collaborative Study Group who contributed to steps 1 and 6.

Step 1: Delphi survey regarding CRI_{cSLE}. The 13 expert participants in the consensus conference and 100 of the pediatric rheumatologists who contributed to the development of other cSLE criteria sets (6,8) received a Delphi survey inquiring about cSLE (1) characteristics and changes in cSLE-CRVs that would support the presence of CRI_{cSLE}. The Delphi survey was piloted (HBR, PöA). Principles and recommendations for the design and conduct of online surveys were followed (16).

Step 2: patient profile ratings prior to the consensus conference. Using prospective data for cSLE patients in the Cincinnati Children's Hospital Medical Center Lupus Registry (17), the PRINTO Lupus Cohort (6), and a multicenter North American cSLE cohort (grant U01-AR-5868 to Dr. Brunner, Principal Investigator), we developed 1,482 unique patient profiles. After omitting patient profiles with >2 missing data elements and some patient profiles without changes in cSLE-CRVs between visits, there were 433 unique patient profiles. Missing observations in these 433 patient profiles were imputed using multiple imputation methods and expectation–maximization algorithms in computation (18–20).

Each patient profile provided the following patient data at the time of a baseline visit and a follow-up visit: 1) physician assessment of cSLE activity (MD-global) as measured on a visual analog scale (VAS) (0 = inactive disease and 10 = very active disease), 2) parent assessment of patient overall well-being (patient-global) as measured on a VAS (0 = very poor and 10 = very well), 3) proteinuria, measured by timed urine collection or protein-to-creatinine ratio in a spot urine specimen, 4) erythrocyte sedimentation rate (ESR), 5) levels of complement C3 and C4, 6) item and summary scores of the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) (21), and 7) the Child Health Questionnaire (version P50) physical summary score (CHQ-PhS) (5,6). Information about complete blood cell counts with differential, serum chemistry, ESR, urinalysis, and anti–double-stranded DNA antibody concentrations were also provided.

Thirteen cSLE experts (HIB, MWB, SPA, SA, CAS, FF, BG, SEW, DML, AR, RK, TA, and MKG) who were voting participants at a consensus conference were asked to rate 200 of the 433 patient profiles prior to the meeting. After the consensus conference, these cSLE experts plus 200 pediatric rheumatologists who previously participated in a similar patient profile rating exercise (6–8) were asked to rate 50 patient profiles each that were randomly selected from the pool of 433 patient profiles. Each patient profile rater was asked to assess the disease course (Question A), using the following response options: major improvement, moderate improvement, minor improvement, unchanged or worse, or "I do not have enough information to make this assessment." Further, if a patient profile rater considered improvement to be present, then he/she was asked whether or not improvement constituted CRI_{cSLE} (Question B). In this context, minor improvement can be considered equivalent to "any improvement" in cSLE. The survey source data were batch-processed, and open source online survey software, REDCap, was used for response management and as a presentation layer (see https://www.project-redcap.org/).

The minimum number of rater responses to each patient profile was 16, and all patient profiles were considered in the subsequent adjudication process. Considering that patient profile raters may not necessarily agree on the interpretation of the disease course for a given patient profile, the "true" overall course of cSLE for a

given patient profile was adjudicated using majority rule (i.e., the majority of the raters of a patient profile agreed on a given disease course). Other rules were calculated, including the 67% rule (i.e., at least two-thirds of the raters agreed on a given disease course. Irrespective of the rule used, results were similar to the majority rule. Hence, we present mainly the results from majority rule analyses.

Three statistical strategies were used to develop a series of candidate criteria to measure CRI_{cSLE}. We considered the PRINTO/ACR provisional criteria for response to therapy (9), which have been previously validated to measure improvement in cSLE (strategy 1). Furthermore, we developed algorithms that considered absolute change (strategy 2) or relative or percentage changes (strategy 3) in the cSLE-CRVs between baseline and follow-up, using multinomial logistic regression. Strategies 2 and 3 yield a numeric "CHILI score" (or log odds of improvement) calculated from the combined changes in the cSLE-CRV predictors between baseline and follow-up (9,22).

The accuracy of the PRINTO/ACR provisional criteria for response to therapy was tested using kappa statistics. With respect to the criterion standard (here, adjudicated disease course from the patient profile ratings), kappa values can be interpreted as follows: poor agreement, $\kappa < 0.4$; fair to good agreement, $\kappa = 0.4$–0.75; and substantial to excellent agreement, $\kappa > 0.75$. For each of the candidate CRI_{cSLE} algorithms from multinomial regression analysis, diagnostic accuracy was assessed by receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC; range 0–1) was calculated, and the diagnostic accuracy was considered outstanding, excellent, good, fair, or poor if the AUC was in the range of 0.9–1.0, 0.81–0.90, 0.71–0.80, 0.61–0.70, and <0.60, respectively (23).

Based on prior consensus (step 3), threshold CHILI scores reflect the highest conditional AUC among all candidate thresholds on the ROC curve, i.e., the point on the ROC curve with the highest precision of correctly classifying the degree of cSLE improvement level (CRI_{cSLE} minor, moderate, or major).

All analyses were conducted using SAS 9.4 and Systat 12 software. *P* values less than 0.05 were considered significant.

Step 3: consensus definition of CRI_{cSLE}. Participants in the consensus conference were experienced pediatric rheumatologists and nephrologists from South America, North America, Asia, and Europe who had substantial clinical and research experience in cSLE. PRINTO leadership (NR) participated in the discussions during the consensus conference as a non-voting content expert. A priori, the consensus level at the consensus conference was set at 75%, i.e., comparable or even somewhat higher than that chosen in previous similar studies (6,13,24). Using nominal group technique guided by an experienced moderator (BMF), the expert panel reached agreement around the definition of CRI_{cSLE}.

The panel also reviewed the performance of the provisional PRINTO/ACR criteria of response to therapy and candidate improvement algorithms derived by multinomial logistic regression using patient profile ratings from step 2, considering the Outcome Measures in Rheumatology filter (25–27): 1) feasibility, i.e., practicability: can the items be measured easily?; 2) reliability, i.e., reproducibility: can the items be measured precisely?; 3) redundancy: are there 2 or more items included in the candidate criteria measuring the same aspect of the disease?; 4) face validity, i.e., credibility: are the criteria sensible?; 5) content validity, i.e., comprehensiveness: do the criteria sample all of the domains of the disease?; 6) criterion validity: based on AUC, do the criteria accurately approximate the "gold standard," i.e., the adjudicated disease course as majority rule?; 7) sensitivity and specificity: do the criteria effectively identify patients with CRI_{cSLE} and/or various levels of improvement and distinguish them from patients who have not experienced CRI_{cSLE} and/or various levels of improvement?; and 8) discriminant validity: do the criteria detect the smallest clinically important change?: i.e., discriminate patients with one of the following disease courses: CRI_{cSLE}; minor improvement, moderate improvement, major improvement, unchanged or worse.

Step 4: second round of patient profile ratings. Besides individuals who were invited to participate in steps 1 and 2, the 433 patient profiles were then sent to another 100 pediatric rheumatologists who previously participated in a similar study (7). Therefore, a total of 213 patient profile raters received 50 randomly selected patient profiles each; formats, response options, and adjudication were described in step 2. The resulting data set was divided, in the sequence of acquisition, into a training data set and a validation data set.

Steps 5 and 6: development and preliminary validation of the CHILI. Using the training data set (step 4), we newly developed candidate algorithms to measure improvement (CRI_{cSLE}; minor, moderate, or major) as described in step 2. In these algorithms, CRI_{cSLE} was considered to be a special threshold score among many possible improvement scores. Threshold scores were transformed to range between 0 and 100. The algorithms and thresholds developed in the training data set (step 5) were validated using the validation data set to derive preliminary CHILI criteria (step 6).

Step 7: ranking of preliminary CHILI algorithms after the consensus conference. The analyses from steps 5 and 6 were presented to the consensus conference participants who had voting rights. These cSLE experts were asked whether, in the setting of a clinical trial, 1) use of CRI_{cSLE} algorithms from multinomial logistic regression was preferable to the use of the PRINTO/ACR provisional criteria for response to therapy 2) absolute differences in the cSLE-CRVs were superior to percentage changes when measuring CRI_{cSLE}, and 3) these algorithms were useful for categorizing the degree of improvement (minor, moderate, or major) in cSLE.

Table 1. Description of 433 patient profiles used in step 4 using the majority rule*

	Training data set (n = 200)		Validation data set (n = 233)	
Patient profile details	Baseline visit	Follow-up visit	Baseline visit	Follow-up visit
SLEDAI items†				
Seizure	3 (1.5)	0 (0.0)	4 (1.7)	0 (0.0)
Psychosis	4 (2.0)	0 (0.0)	5 (2.2)	0 (0.0)
Organic brain syndrome	7 (3.5)	1 (0.5)	9 (3.9)	2 (0.9)
Visual disturbance	4 (2.0)	1 (0.5)	4 (1.7)	1 (0.4)
Cranial nerve involvement	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lupus headaches	12 (6.0)	2 (1.0)	15 (6.4)	2 (0.9)
Cardiovascular accidents	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Vasculitis	27 (13.5)	6 (3.0)	25 (10.7)	6 (2.6)
Arthritis	80 (40.0)	22 (11.0)	96 (41.2)	19 (8.2)
Myositis	4 (2.0)	2 (1.0)	9 (3.9)	4 (1.7)
Urinary casts	30 (15.0)	9 (4.5)	38 (16.3)	7 (3.0)
Hematuria	71 (35.5)	31 (15.5)	100 (42.9)	30 (12.9)
Proteinuria	90 (45.0)	49 (24.5)	82 (35.2)	52 (22.3)
Leukocyturia	44 (22.0)	20 (10.0)	66 (28.3)	20 (8.6)
Rash	81 (40.5)	26 (13.0)	100 (42.9)	27 (11.6)
Alopecia	42 (21.0)	13 (6.5)	50 (21.5)	15 (6.4)
Mucosal ulcers	42 (21.0)	9 (4.5)	50 (21.5)	12 (5.2)
Pleurisy	8 (4.0)	2 (1.0)	15 (6.4)	4 (1.7)
Pericarditis	8 (4.0)	1 (0.5)	14 (6.0)	0 (0.0)
Low complement levels	154 (77.0)	116 (58.0)	174 (74.7)	128 (54.9)
Positive anti-dsDNA antibodies	155 (77.5)	109 (54.5)	175 (75.1)	119 (51.1)
Fever	42 (21.0)	5 (2.5)	46 (19.7)	3 (1.3)
Thrombocytosis	12 (6.0)	2 (1.0)	13 (5.6)	4 (1.7)
Leukopenia	27 (13.5)	7 (3.5)	39 (16.7)	8 (3.4)
SLEDAI summary score‡	14.0 ± .5/13.0 (2.0, 39.0)	5.9 ± 5.1/4.0 (0.0, 31.0)	14.2 ± 8.1/13.0 (0.0, 39.0)	5.3 ± 4.7/4.0 (0.0, 31.0)
Laboratory testing‡				
ESR	48.8 ± 35.2/40.0 (1.0, 180)	25.5 ± 18.9/21.0 (2.0, 103)	47.6 ± 37.8/40.0 (1.0, 180)	24.3 ± 17.2/21.0 (1.0, 101)
UPCR	1.3 ± 2.2/0.3 (0.0, 13.2)	0.5 ± 1.1/0.2 (0.0, 7.8)	1.2 ± 2.3/0.2 (0.0, 13.2)	0.5 ± 1.2/0.2 (0.0, 7.8)
Other assessments‡				
MD-global	4.2 ± 2.9/4.1 (0, 10)	1.7 ± 2.1/0.8 (0, 10)	5.0 ± 2.6/5.0 (0, 10)	1.8 ± 1.8/1.1 (0, 8.6)
Patient-global	3.0 ± 3.0/1.9 (0, 10)	1.4 ± 2.0/0.6 (0, 10)	4.8 ± 3.3/5.0 (0, 10)	3.3 ± 3.5/1.7 (0, 10)
CHQ-PhS	36.8 ± 15.5/40.4 (1.0, 58.7)	45.4 ± 11.5/49.4 (5.5, 59.7)	36.9 ± 14.7/40.3 (1.0, 58.7)	44.6 ± 11.7/48.4 (10.3, 59.7)

* SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; anti-dsDNA = anti–double-stranded DNA; ESR = erythrocyte sedimentation rate; UPCR = proteinuria, measured by timed urine collection or protein-to-creatinine ratio in a spot urine specimen; MD-global = physician assessment of childhood-onset SLE as measured on a visual analog scale (VAS) (0 = inactive disease, 10 = very active disease); patient-global = global assessment of patient well-being, measured on a VAS (0 = very poor; 10 = very well); CHQ-PhS: Child Health Questionnaire (parent version P50) physical function summary score

† Values are the number (%).

‡ Values are the mean ± SD/median (minimum, maximum).

RESULTS

Definition of CRI_{cSLE}. The survey (step 1) inquired about changes in cSLE-CRVs, signs, and symptoms that would support the presence of CRI_{cSLE}. Among the 113 pediatric rheumatologists and nephrologists approached for survey participation, 92 (81%) responded. Survey participants from different regions or less versus more than 10 years of experience in treating cSLE did not differ significantly in their responses (data not shown). There was ≥80% agreement that, with CRI_{cSLE}, the MD-global and/or the score for a disease activity index must be better or unchanged and that patients with CRI_{cSLE} could experience new organ involvement as long as it did not involve the neuropsychiatric, hematologic, gastrointestinal, renal, ophthalmologic, or cardiopulmonary organ system. The initial ratings of 200 patient profiles provided additional data regarding the measurement of CRI_{cSLE} (see Supplementary Table 1 [available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23834/abstract] for adjudication results). After review of this information during the consensus conference (step 3), there was 100% agreement for the following consensus definition of CRI_{cSLE}: "A clinically relevant improvement has occurred in a child with lupus if there are reduced signs of disease from active lupus. Although there may not be improvement of lupus activity in all organ systems, there cannot be increased lupus activity in a major organ system, i.e., neuropsychiatric hematological, gastrointestinal, renal, ophthalmological, or cardiopulmonary organ system. Patient symptoms will be at least stable, and immunosuppressive therapy should be unchanged or decreased." Further, cSLE experts concluded that further testing of the PRINTO/ACR provisional criteria for response to therapy in cSLE was warranted, and that multinomial logistic regression modeling should be pursued to measure CRI_{cSLE} with threshold choice at the statistical optimal point on the AUC (≥92% agreement for both).

Post–consensus conference patient profile ratings. As part of step 4, the 433 patient profiles were sent to 213 patient profile raters. The response rate was 91% (194 of 213), and all 433 patient profiles qualified for adjudication. The resulting data set was split into a training data set (200 patient profiles) and a validation data set (n = 233). Baseline characteristics of the patients represented in these data sets are shown in Table 1. When the majority rule was applied, there were 95 (47.5%) patient profiles without CRI_{cSLE} and 105 patient profiles (52.5%) with CRI_{cSLE} in the training data set. Among patient profiles adjudicated to reflect CRI_{cSLE}, 83% were considered to represent moderate or major improvement of cSLE, while 99% of patient profiles without CRI_{cSLE} were adjudicated to reflect, at most, minor improvement in cSLE.

Performance of individual cSLE-CRVs to measure CRI_{cSLE}. Based on univariate logistic regression in the training data set, absolute changes and percentage (or relative) changes in the cSLE-CRVs had similar discriminative properties to detect CRI_{cSLE} (Table 2). However, only absolute changes in the urine protein-to-creatinine ratio ($P < 0.001$) between baseline and follow-up but not percentage changes

Table 2. Discriminative properties of absolute and relative (percentage) changes in the cSLE core response variable for capturing CRI_{cSLE} in the training data set*

Core response variables	CRI_{cSLE}			AUC	Sensitivity†	Specificity†	Threshold score‡
	No	Yes	*P*				
Absolute difference§							
UPCR	−0.21 ± 0.18	−1.16 ± 0.17	<0.0001	0.65	33.33	90.53	−0.81
SLEDAI	−2.71 ± 0.57	−13.01 ± 0.54	<0.0001	0.93	94.29	82.11	−5.00
MD-global	−0.65 ± 0.21	−4.23 ± 0.20	<0.0001	0.90	94.29	67.37	−1.00
Patient-global	−0.06 ± 0.31	−2.89 ± 0.29	<0.0001	0.76	70.48	78.95	−0.80
CHQ-PhS	2.01 ± 1.32	14.55 ± 1.26	<0.0001	0.77	70.48	81.05	5.15
Percentage difference¶							
UPCR	33 ± 30	−30 ± 29	0.132	0.67	60.95	69.47	−0.41
SLEDAI	−24 ± 3	−72 ± 3	<0.0001	0.91	84.76	89.47	−0.52
MD-global	−10 ± 3	−63 ± 3	<0.0001	0.91	84.76	86.32	−0.47
Patient-global	31 ± 12	−33 ± 12	<0.0001	0.77	72.38	77.89	−0.23
CHQ-PhS	20 ± 28	151 ± 27	0.001	0.76	69.52	81.05	0.13

* Values for sensitivity and specificity are the percent. cSLE = childhood-onset systemic lupus erythematosus; CRI_{cSLE} = clinically relevant improvement in cSLE (see Table 1 for other definitions).
† Sensitivity and specificity calculated at the threshold score.
‡ Optimal score from univariate logistic regression to discriminate between the presence versus absence of CRI_{cSLE}.
§ Values are the mean ± SD from absolute differences between the baseline and follow-up time points.
¶ Values are the percentage change at the time of the follow-up visit relative to the baseline visit.

(P = 0.132) significantly differed between patients with and those without CRI_{cSLE}. Compared with the other cSLE-CRVs but irrespective of the type of change (absolute, relative) considered, the urine protein-to-creatinine ratio had only fair accuracy (AUC ≤ 0.67) for capturing CRI_{CSLE}. Individually, the MD-global and the SLEDAI had the highest accuracy (AUC ≥ 0.90 for both) for identifying CRI_{CSLE} status.

Performance of the PRINTO/ACR provisional criteria for response to therapy to measure CRI_{cSLE}. As shown in Table 3 and Supplementary Table 2 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23834/abstract), in both the training data set and validation data set, the PRINTO/ACR provisional criteria for response to therapy had, at most, fair accuracy for capturing CRI_{cSLE} status ($\kappa \leq 0.3$ for the majority rule and $\kappa \leq 0.43$ for the 67% rule). The same was also true for measuring various levels of improvement ($\kappa < 0.34$ for both the majority rule and the 67% rule).

Development of the CHILI to measure CRI_{cSLE}. As part of the step 5 analyses (Table 4), we used multinomial regression to generate candidate algorithms using the cSLE-CRVs that have

Table 3. Performance of the PRINTO/ACR/EULAR criteria for cSLE improvement*

Reference standard (vs. no change)	PRINTO/ACR/EULAR provisional criteria for response to therapy†	Development data set (n = 200)			Validation data set (n = 233)		
		Sensitivity	Specificity	Kappa ± SE‡	Sensitivity	Specificity	Kappa ± SE‡
CRI_{cSLE}	2/5 by ≥50% and no more than 1 worse by >30% (DI11)	91.4	37.9	0.30 ± 0.06	84.7	50.6	0.37 ± 0.06
	2/5 by ≥40% and no more than 1 worse by >30% (DI08)	91.4	37.9	0.30 ± 0.06	84.7	50.6	0.37 ± 0.06
	2/5 by ≥40% and no more than 1 worse by >30% (DI17)	91.4	37.9	0.30 ± 0.06	84.7	50.6	0.37 ± 0.06
	3/5 by ≥30% and no more than 2 worse by >30% (DI12)	100.0	11.6	0.12 ± 0.03	97.3	15.3	0.15 ± 0.05
At least minor improvement	2/5 by ≥50% and no more than 1 worse by >30% (DI11)	89.6	47.7	0.41 ± 0.07	81.8	48.7	0.32 ± 0.07
	2/5 by ≥40% and no more than 1 worse by >30% (DI08)	89.6	47.7	0.41 ± 0.07	81.8	48.7	0.32 ± 0.07
	2/5 by ≥40% and no more than 1 worse by >30% (DI17)	89.6	47.7	0.41 ± 0.07	81.8	48.7	0.32 ± 0.07
	3/5 by ≥30% and no more than 2 worse by >30% (DI12)	99.3	15.4	0.19 ± 0.06	97.5	17.1	0.18 ± 0.05
At least moderate improvement	2/5 by ≥50% and no more than 1 worse by >30% (DI11)	90.9	33.0	0.22 ± 0.05	87.5	40.5	0.26 ± 0.05
	2/5 by ≥40% and no more than 1 worse by >30% (DI08)	90.9	33.0	0.22 ± 0.05	87.5	40.5	0.26 ± 0.05
	2/5 by ≥40% and no more than 1 worse by >30% (DI17)	90.9	33.0	0.22 ± 0.05	87.5	40.5	0.26 ± 0.05
	3/5 by ≥30% and no more than 2 worse by >30% (DI12)	100.0	9.8	0.09 ± 0.03	99.0	12.2	0.10 ± 0.03
Major improvement	2/5 by ≥50% and no more than 1 worse by >30% (DI11)	93.8	27.6	0.12 ± 0.03	91.9	31.8	0.10 ± 0.03
	2/5 by ≥40% and no more than 1 worse by >30% (DI08)	93.8	27.6	0.12 ± 0.03	91.9	31.8	0.10 ± 0.03
	2/5 by ≥40% and no more than 1 worse by >30% (DI17)	93.8	27.6	0.12 ± 0.03	91.9	31.8	0.10 ± 0.03
	3/5 by ≥30% and no more than 2 worse by >30% (DI12)	100.0	7.2	0.04 ± 0.01	100.0	8.6	0.03 ± 0.01

* The table was adapted from reference 9 (Ruperto et al, 2006). Values for sensitivity and specificity are the percent. PRINTO = Pediatric Rheumatology International Trials Organization; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; cSLE = childhood-onset systemic lupus erythematosus; CRI_{cSLE} = clinically relevant improvement in cSLE (see Table 1 for other definitions).
† The 4 highest-ranking algorithms (DI11, DI08, DI17, DI12) are shown. Ratio (n/m) designates the number of the 5 cSLE core response variables CRVs (MD-global, patient-global, Disease Activity Score, urine protein-to-creatinine ratio from spot urine or estimated by 24-hour timed urine collection) with improvement.
‡ The kappa value provides agreement between the provisional PRINTO/ACR/EULAR criteria for response to therapy and patient profile ratings from step 2, adjudicated using the majority rule.

been considered relevant for capturing improvement of cSLE (6,22). Irrespective of the type of change, i.e., absolute or percentage differences in the cSLE-CRVs between baseline and follow-up, algorithms had similar accuracy (AUC) for measuring CRI_{cSLE}. For example, using the algorithm that considered absolute changes in the cSLE-CRVs, a logit score of 0.16 or, after transformation to a scale of 0 to 100, a CHILI score of 54 was 89.5% sensitive and 92.6% specific for capturing CRI_{cSLE} status correctly (AUC 0.97) in the development data set. When considering percentage changes in the cSLE-CRVs between visits in the algorithm instead, a CHILI score of 60 had similar measurement properties (AUC 0.96, sensitivity 87.6%, specificity 92.6) for capturing CRI_{cSLE} status (Figure 2).

Initial validation of the CHILI algorithms. Algorithms considering absolute changes rather than percentage changes in the cSLE-CRVs were similarly robust, i.e., they maintained their accuracy (AUC) similarly well as the validation data set. Using the model parameters and threshold scores obtained from the training data set, the AUC of discrimination between patients who had CRI_{cSLE} as compared to those who did not was 0.93 (Figure 2). Hence, a CHILI score of 54 (absolute changes in the cSLE-CRVs are considered) represents the optimal threshold score based on the training data set. This CHILI score of 54 is 81.1% sensitive and 84.2% specific for CRI_{cSLE} in the validation data set.

Use of the CHILI to identify minor, moderate, and major response to cSLE therapy. As shown in Figure 2 and Table 4, the CHILI algorithms developed and validated to measure CRI_{cSLE} were also excellent for discriminating patients with various levels of improvement (minor, moderate, or major) between baseline and follow-up. Again, algorithms considering absolute differences and percentage differences in the cSLE-CRVs between baseline and follow-up performed similarly well in both the training data set and the validation data set.

Ranking of the candidate CHILI algorithms. The results for performance of the PRINTO/ACR provisional criteria for response to therapy, CHILI algorithms considering percentage change, and

Table 4. Absolute versus relative (or percentage) changes of the combination of the cSLE core response variable for capturing CRI_{CSLE} and various levels of improvement†

Level of response to therapy or improvement	Type of CRV change considered	Development data set					Validation data set		
		AUC	Sensitivity*	Specificity*	Threshold improvement logit score	Threshold improvement score (0–100)	AUC	Sensitivity	Specificity
CRI_{CSLE}	Absolute	0.97	89.5%	92.6%	**0.16**	**54**	0.93	81.1%	84.2%
	Percentage	0.96	87.6%	92.6%	**0.39**	**60**	0.92	81.1%	87.1%
At least minor improvement	Absolute	0.95	91.1%	87.7%	**–1.77**	**15**	0.93	93.1%	73.9%
	Percentage	0.93	85.9%	89.2%	**–1.15**	**24**	0.93	90.2%	76.1%
At least moderate improvement	Absolute	0.97	96.6%	88.4%	**0.76**	**68**	0.95	93.6%	79.5%
	Percentage	0.96	88.6%	92.9%	**1.33**	**79**	0.93	85.0%	84.8%
Major improvement	Absolute	0.97	100%	85.5%	**2.48**	**92**	0.92	93.6%	73.4%
	Percentage	0.95	91.7%	84.9%	**2.46**	**92**	0.94	98.4%	77.7%
CHILI‡ using absolute changes (Δ) of cSLE-CRVs	Improvement Logit Score (y)= - (5.1 + 0.47 x ΔSLEDAI + 0.7 x ΔMD-global + 1.1x Δ UPCR + 0.32 x ΔPatient-global - 0.002x ΔCHQ-PhS) Improvement Score (0-100) = 100• {EXP(y) / [1+EXP(y)]}								
CHILI‡ using percentage changes ($\Delta_{\%}$) of cSLE-CRVs	Improvement Logit Score (y) = - (6.1 + 6.5x $\Delta_{\%}$SLEDAI + 6.1X $\Delta_{\%}$MD-global + 0.02x $\Delta_{\%}$UPCR + 0.48x $\Delta_{\%}$Patient-global - 0.43x $\Delta_{\%}$CHQ-PhS) Improvement Score (0-100) = 100• {EXP(y) / [1+EXP(y)]}								

* Predictors used in a multivariate logistic model can be either from absolute differences between the baseline and follow-up time points OR percentage changes at the time of follow-up relative to the baseline visit in the development data set. An improvement logit score can be converted into an improvement score (range 0–100) using the formula: Improvement Score = 100*EXP(Improvement logit score)/[1+ EXP(Improvement logit score)]. Either a higher (or lower) improvement logit score or improvement score indicates higher (lower) likelihood of improvement. For a classification purpose, a patient's improvement score can be compared against the threshold score.
† Majority rule; Δ change score between baseline and follow-up visits.
‡ Improvement logit scores were calculated using multivariate logistic models. UPCR: urine protein to creatinine ratio from random urine sample; SLEDAI: SLE disease activity summary score; MD-global: physician global assessment of cSLE activity; Patient-global: patient assessment of overall well-being; CHQ-PHS Child Health Questionnaire, P50 version Physical function summary score.

CHILI algorithms considering absolute changes in the cSLE-CRVs were presented to the consensus conference participants who had voting rights. There was consensus (100%) that the CHILI algorithms were preferable to the PRINTO/ACR provisional criteria for response to therapy to measure CRI_{cSLE} as well as various levels of improvement in clinical trials of cSLE. Furthermore, CHILI algorithms using absolute changes were favored over those using percentage changes in the cSLE-CRVs, given their ease of use. Although scaling to a range of 0 to 100 was favored, there were some concerns that transformation might be mathematically challenging.

DISCUSSION

This international study investigated clinically important improvement in children with cSLE. In addition to a consensus definition of CRI_{cSLE}, we developed and initially validated the CHILI to serve as provisional criteria to measure CRI_{cSLE}. A composite measure to capture CRI_{cSLE} is necessary, because there is no single sign, clinical test, or patient symptom that is adequately sensitive and simultaneously specific for the presence of CRI_{cSLE}. Furthermore, we confirm that the CHILI is able to accurately describe the degree of cSLE improvement.

Several pediatric rheumatology response measures, such as the JIA-ACR30 criteria to capture response to therapy with JIA, consider relative (or percentage) changes in core response variables. While CHILI algorithms using percentage and absolute changes performed similarly in terms of accuracy, sensitivity, and specificity at the proposed threshold scores, we consider CHILI scores calculated from absolute changes in the cSLE-CRVs to be easier to compute, hence preferable. This is consistent with

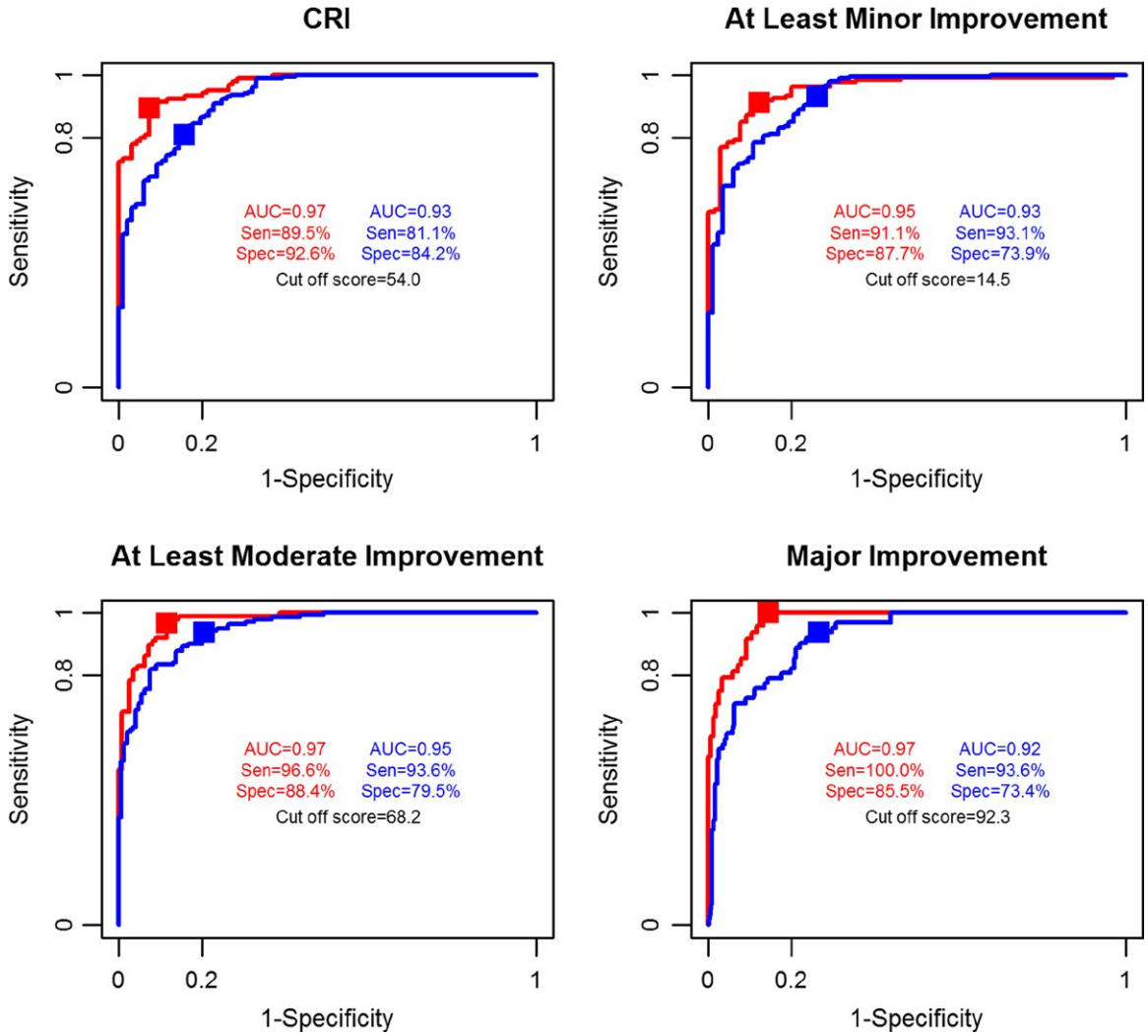

Figure 2. Performance of Childhood Lupus Improvement Index (CHILI) when considering absolute of the cSLE core response variables between baseline and follow-up in the development data set and the validation data set. The accuracy of the CHILI algorithm is largely maintained in the validation data set (blue) as compared to the training data set (red). As shown in panel labeled CRI a CHILI score of 54 (range 0–100) was 81.1% sensitive (Sen) and 84.5% specific (Spec) in the validation data set to capture CRI_{cSLE}, with an overall accuracy (area under the receiver operating characteristic curve [AUC]) of 0.93. CHILI algorithms developed and validated to measure CRICSLE were also excellent in discriminating patients with various levels of improvement (minor, moderate, major) between baseline and follow-up. CRI = clinically relevant improvement (see Figure 1 for other definitions).

the recently published ACR provisional criteria for global flares in cSLE (7,28). Indeed, more complex mathematical maneuvers beyond addition and multiplication are avoided, which is different from the Disease Activity Score in 28 joints, which includes a square root calculation, for example (29). For reasons associated with scaling, we transformed the CHILI scores to range from 0 to 100, with higher scores reflecting a larger degree of improvement. Whether such mathematical transformation maneuvers improve the ease of use of the CHILI will need to be studied in the future.

Different from the ACR provisional criteria for global flares in cSLE (7), the CHILI considers patient perspectives more comprehensively. Specifically, changes in patient overall well-being and physical function (CHQ-PhS) are included in the algorithm. This is consistent with the results of earlier discussions of how to capture response to therapy in cSLE (6,8).

Currently, the SRI is the principal outcome measure used in clinical trials in adults with SLE. We have shown that the PRINTO/ACR provisional criteria for response to therapy in cSLE (9) are more accurate than the SRI in capturing improvement in cSLE (10). In the current study, we confirmed that the PRINTO/ACR provisional criteria for response to therapy seem to have, at best, fair accuracy for capturing the true course of cSLE, including CRI_{cSLE}. Different from the CHILI, in the PRINTO/ACR provisional criteria for response to therapy all cSLE-CRV changes are considered equally (same percentage changes) relevant for measuring response to therapy. However, from a measurement point of view, as supported by the consensus definition for CRI_{cSLE} and our univariate analysis, the cSLE-CRVs have differential importance to clinicians when judging the disease course in a child with cSLE (10). Taken together, the PRINTO/ACR provisional criteria for response to therapy—and by extension the SRI—can be used in clinical trials of cSLE but likely require sample sizes larger than those using the CHILI to capture response to therapy.

A limitation of our study might be that we were unable to test whether consideration of the British Isles Lupus Activity Group index (30) or other disease activity indices instead of the SLEDAI as a measure of cSLE activity would have allowed us to accurately identify cSLE patients who experienced CRI_{cSLE}. Indeed, the cSLE-CRVs do not specify which validated measures of cSLE activity are considered for the assessment of patients' response to therapy (9). We used the SLEDAI, given its ease of use and widespread acceptance around the world. Additional research will be required to assess whether other disease activity index scores can be used interchangeably. In addition, we did not provide patient profile raters with consensus definitions of what constitutes minor, moderate, and major improvement. Nonetheless, the accuracy of the CHILI algorithm performed well in the data sets used in this study. Last, we focused on the majority rule to adjudicate the disease course presented in the various patient profiles, which might have introduced bias. However, use of the 67% rule yielded results comparable to those using the CHILI.

The ACR has outlined a series of validation steps necessary before new criteria are to be widely used for clinical care or research (15,31). One step is to use data from clinical trials to develop response criteria. However, such data from interventions that impact cSLE activity currently are unavailable. Thus, we used the patient profile raters' perceptions of the course of cSLE instead. Given the prospective character of our data and the expertise of the patient profile raters, we considered the quality of the training data set and the validation data set to be high, and the number of patient profiles to assess CRI_{cSLE} yielded a robust CHILI.

In summary, a methodologically stringent process was used to develop a novel index to measure global improvement or response to therapy in cSLE. This provisional CHILI instrument can be used to help identify children with cSLE who have experienced a clinically relevant improvement and to categorize the degree of improvement as minor, moderate, or major. However, additional testing in independent data sets is required to confirm the performance characteristics of the CHILI when used in cSLE.

ACKNOWLEDGEMENTS

We thank Kasha Wiley (overall study coordination), Susan Priest (consensus conference logistics), Carly Muller, Malea Rolfsen, Allen Watts, Gaurav Gulati, and Jamie Meyers-Eaton (patient profile testing) from Cincinnati Children Hospital Medical Center (CCHMC) as well as CCHMC Biomedical Informatics (web-based data management application development). We are indebted to the members of the External Scientific Advisory Committee of this study for their advice regarding study implementation, conduct, and statistical analysis: Drs. Tuhina Neogi, Ian Bruce, David Isenberg, Nicola Ruperto, and James Witter.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Brunner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Brunner, Ying.

Acquisition of data. Brunner, Holland, Beresford, Adroit, Appenzeller, Silva, Flores, Goliad, Avar Ayden, Wanderer, Levy, Ravelli, Khubchandani, Avcin, Klein-Gitelman, Ruperto, Feldman, Ying.

Analysis and interpretation of data. Brunner, Ying.

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APPENDIX A. Members of the Pediatric Rheumatology Collaborative Study Group and PRINTO Who Served as Patient Profile Raters

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(India) Amita Aggarwal, Sujata Sawhney; (Israel) Yonatan Butbul Aviel; (Italy) Rolando Cimaz, Maria Cristina Maggio; (Latvia) Ingrid Rumba-Rozenfelde; (Libya) Soad Hashad; (Malaysia) Sern Chin Lim; (Mexico) Carlos Abud, Ruben Burgos-Vargas, Roberto Carreño-Manjarrez, Sandra Enciso Pelaez, Hayde Hernandez-Huirache, Rocio Maldonado Velázquez, Javier Orozco, Ana Luisa Rodriguez-Lozano, Omar Ernesto Rojas Pacheco, Luz Maria Suárez Larios, Gabriel Vega, Julia Verónica Ramírez Miramontes, Ivon Karina Ruíz Lopez; (Netherlands) Sylvia Kamphuis, Dieneke Schonenberg-Meinema; (New Zealand) Anthony Concannon, Jaqueline Yan; (Nicaragua) Martha Jarquin Jaime; (Oman) Safiya Al Abrawi; (Paraguay) Cynthia Vega, Jorge Lopez-Benitez; (Peru) Amparo Ibáñez Estrella, Tatiana Miraval; (Philippines) Leonia Dans, Karen Joy Kimseng; (Poland) Violetta Opoka-Winiarska, Lidia Rutkowska-Sak, Elzbieta Smolewska; (Portugal) Marta Conde, Margarida Guedes; (Puerto Rico) Enid del Valle, Ana Quintero-Del Rio; (Romania) Constantin Ailioaie, Mihaela Sparchez; (Russian Federation) Ekaterina Alekseeva, Vladimir Keltsev; (Saudi Arabia) Sulaiman Al-Mayouf, Abdurhman Asiri, Wafaa Suwairi; (Serbia) Gordana Susic, Gordana Vijatov-Djuric; (Singapore) Elizabeth Ang, Thaschawee Arkachaisri; (Spain) Alina-Lucica Boteanu, Juan Carlos Lopez-Robledillo, Marta Medrano San Ildefonso, Consuelo Modesto, Inmaculada Calvo; (Sweden) Jorge Sotoca-Fernandez; (Switzerland) Isabel Bolt; (Thailand) Soamarat Vilaiyuk; (United Kingdom) Eslam Al-Abadi, Eileen Baildam, Lampros Fotis, Clare Pain, Clarissa Pilkington; (United States) Khalid Abulaban, Fatima Barbar-Smiley, Bryce Binstadt, John Bohnsack, Alexis Boneparth, Diane Brown, Peter Chira, Randy Cron, Fatma Dedeoglu, Anne Eberhard, Abraham Gedalia, Alexei Grom, Beatrice Goilav, Michael Henrickson, Christine Hom, Jennifer Huggins, Rita Jerath, Jordan Jones, Lawrence Jung, Daniel Kingsbury, Jamie Lai, Daniel Lovell, Kabita Nanda, James Nocton, Judyann Olson, Kathleen O'Neil, Karen Onel, Lynn Punaro, Andreas Reiff Kelly Rouster-Stevens, Natasha Ruth, Ken Schikler, Kara Murphy Schmidt, Grant Schulert, Bracha Shaham, Nora Singer, Judith Smith, Robert Sundel, Grant Syverson, Patricia Vega-Fernandez, Richard Vehe, Linda Wagner-Weiner; (Uruguay) Juan Cameto, Rosario Jurado; (Venezuela) Irama Maldonado.

Arthritis Care & Research
Vol. 70, No. 6, June 2018, pp 813–822
DOI 10.1002/acr.23557
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ORIGINAL ARTICLE

American College of Rheumatology Provisional Criteria for Global Flares in Childhood-Onset Systemic Lupus Erythematosus

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Objective. **To validate the preliminary criteria of global flare for childhood-onset SLE (cSLE).**

Methods. **Pediatricians experienced in cSLE care (n = 268) rated unique patient profiles; results of standard cSLE laboratory testing and information about the cSLE flare descriptors were presented as follows: global assessment of patient well-being, physician global assessment of disease activity (MD-global), Disease Activity Index score, protein/creatinine ratio (PCR), and erythrocyte sedimentation rate (ESR). Using rater interpretation of the course of cSLE (baseline versus followup as the gold standard), performance (sensitivity, specificity, area under the receiver operating characteristic curve [AUC]) of the preliminary flare criteria was tested. An international consensus conference was held to rank the preliminary flare criteria as per the American College of Rheumatology recommendations and delineate threshold scores for minor, moderate, and major flares.**

Results. **The accuracy of the 2 highest-ranked candidate criteria that consider absolute changes (Δ) of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) or British Isles Lupus Assessment Group (BILAG) (numeric scoring: A = 12, B = 8, C = 1, and D/E = 0), MD-global, PCR, and ESR were confirmed (both AUC >0.93). For the SLEDAI-based criteria (0.5 × ΔSLEDAI + 0.45 × ΔPCR + 0.5 × ΔMD-global + 0.02 × ΔESR) flare scores ≥6.4/3.0/0.6 constituted major/moderate/minor flares, respectively. For the BILAG-based algorithm (0.4 × ΔBILAG + 0.65 × ΔPCR + 0.5 × ΔMD-global + 0.02 × ΔESR) flare scores ≥7.4/3.7/2.2 delineated major/moderator/minor flares, respectively. These threshold values (SLEDAI, BILAG) were all >82% sensitive and specific for capturing flare severity.**

Conclusion. **Provisional criteria for global flares in cSLE are available to identify patients who experienced a flare. These criteria also allow for discrimination of the severity of cSLE exacerbations.**

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex, chronic, multisystem autoimmune inflammatory disease, with up to 20% of patients diagnosed during childhood (cSLE) (1,2). When disease commences early in life rather than during adulthood, it has a less favorable prognosis, particularly due to multiorgan and kidney involvement (3,4). The course of cSLE is characterized by episodes of disease flares, followed by periods of improvement, generally due to more intensive drug therapy. There is international consensus that a flare of cSLE is "a measurable worsening of disease activity in at least one organ system, involving new or worse signs of disease that may be accompanied by new or worse SLE

Supported by the NIH (grants 5U01-AR-51868, P30-AR-AR47363, and 2UL-1RR-026314) and by LUPUS UK, who supports the UK Juvenile-Onset Systemic Lupus Erythematosus Cohort Study, along with the NIHR Clinical Research Network (CRN), NIHR CRN Children's Specialty Group, and NIHR Alder Hey Clinical Research Facility. Dr. Silva's work was supported by grants from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP 2015/03756-4), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 303422/2015-7), and by Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente" da USP (NAP-CriAd).

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*Correction added after online publication 2 May 2018: The author byline has been corrected to include the name for the PRCSG and PRINTO Investigators.

Significance & Innovations

- Results of the preliminary validation of criteria of global flare for childhood-onset systemic lupus erythematosus are provided.
- Based on the flare scores, mild, moderate, and severe flares can be defined.

symptoms; depending on the severity of the flare, more intensive therapy may be required" (5). Further, using consensus formation techniques, agreement has been achieved regarding preliminary criteria of global flares of cSLE based on changes of the erythrocyte sedimentation rate (ESR), the protein/creatinine ratio (PCR), physician global assessment of cSLE activity (MD-global), and the score of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (6,7) or the British Isles Lupus Activity Group index (BILAG) (8). Moreover, there is consensus around the need to discriminate flares as per their severity: mild/minor, moderate, and major/severe flares (5). However, there are no generally accepted criteria or algorithms to determine how to measure the severity of cSLE flares, nor have the preliminary cSLE flare criteria been validated in an independent data set. Thus, the objectives of this phase of the project were to validate the preliminary criteria of global flare of cSLE and to apply consensus formation methodology to define flare threshold levels for minor, moderate, and major flares. These criteria were created to define cSLE flares and their severity for use in clinical trials.

PATIENTS AND METHODS

The overall approach to this project was based on the methodologic framework successfully employed in pediatric rheumatology criteria measures in the past (9–11), aligned with recommendations of the American College of Rheumatology (ACR) Criteria Subcommittee and the Quality of Care Committee (12). The initial results of the consensus process resulting in preliminary cSLE flare criteria have been described elsewhere (5,13). Briefly, previous research demonstrated that the scores of a disease activity measure alone are inadequate for identifying flares (5). International agreement was reached regarding preliminary criteria to measure global flares of cSLE. Pediatric rheumatologists participated in Delphi surveys that yielded consensus around a common definition of cSLE global flares, and the delineation of cSLE flare descriptors. This was followed by exploration of candidate flare criteria (5) and the identification of preferred algorithms of global cSLE flares (14). Notably, data and analyses all suggested that uniform percentage changes of the cSLE flare descriptors are insufficient to capture cSLE flares with high sensitivity. Further, inclusion of the MD-global assessment of cSLE activity in highly accurate cSLE candidate flare algorithms proved necessary (5,15). During the first consensus conference, the top-performing candidate flare algorithms, derived either from multinomial logistic regression modeling or classification tree analysis (CART), were established.

We now present the phase of the project aimed at validating the preferred preliminary flare algorithms (14) via testing in an independent validation data set (Figure 1). These encompassed patient profile (PP) ratings that were requested from 503 pediatric rheumatologists from Australia, Africa, Asia, Europe, and the Americas who were members of at least 1 of the following organizations: the Pediatric Rheumatology Collaborative Study Group, the Childhood Arthritis Rheumatology Research Alliance, the Pediatric Rheumatology European Society Juvenile Lupus Working Group, and the Pan American League of Associations for Rheumatology (step 1).

The interpretation of the flare or "true" disease course of a given PP was determined using 2 approaches, which resulted in 2 distinct data sets for the subsequent validation exercises (step 2). Using the PP ratings, the preliminary criteria for cSLE global flares were tested for their ability to discriminate patients who experienced different levels of flares (minor, moderate, and major) (step 3). Subsequently, during a consensus conference, the validity of the criteria was critically reviewed, taking into consideration information from the medical literature, statistical performance, reliability, feasibility, and face validity as per the ACR guidance document (12) and the Outcome Measures in Rheumatology filter (16) (step 4).

Preliminary cSLE flare algorithms. We considered the top 4 preliminary flare algorithms (identified in the first consensus conference) based on feasibility, truthfulness, and discrimination (17). Two of the 4 preliminary cSLE flare algorithms (SLEDAI-based criteria: $0.5 \times \Delta\text{SLEDAI} + 0.45 \times \Delta\text{PCR} + 0.5 \times \Delta\text{MD-global} + 0.02 \times \Delta\text{ESR}$, and BILAG-based criteria: $0.4 \times \Delta\text{BILAG} + 0.65 \times \Delta\text{PCR} + 0.5 \times \Delta\text{MD-global} + 0.02 \times \Delta\text{ESR}$) were derived by multinomial logistic regression that considered several of the cSLE flare descriptors, and that yield "flare scores" (or log odds of flare), with a higher score representing a higher likelihood of a flare to have occurred. The other 2 algorithms of the top preliminary flare criteria were derived from CART (SLEDAI-CART: where score = 4 if $3 \leq$ SLEDAI, score = 3 if $0.7 \leq$ PCR and $3 >$ SLEDAI, score = 2 if $2 \leq$ MD-global and $0.7 >$ PCR and $3 >$ SLEDAI, and score = 1 if otherwise, and BILAG-CART: where score = 4 if $2 \leq$ BILAG, score = 3 if $0.7 \leq$ PCR and $2 >$ BILAG, score = 2 if $2 \leq$ MD and $0.7 >$ PCR and $2 >$ BILAG,

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Submitted for publication July 8, 2017; accepted in revised form March 8, 2018.

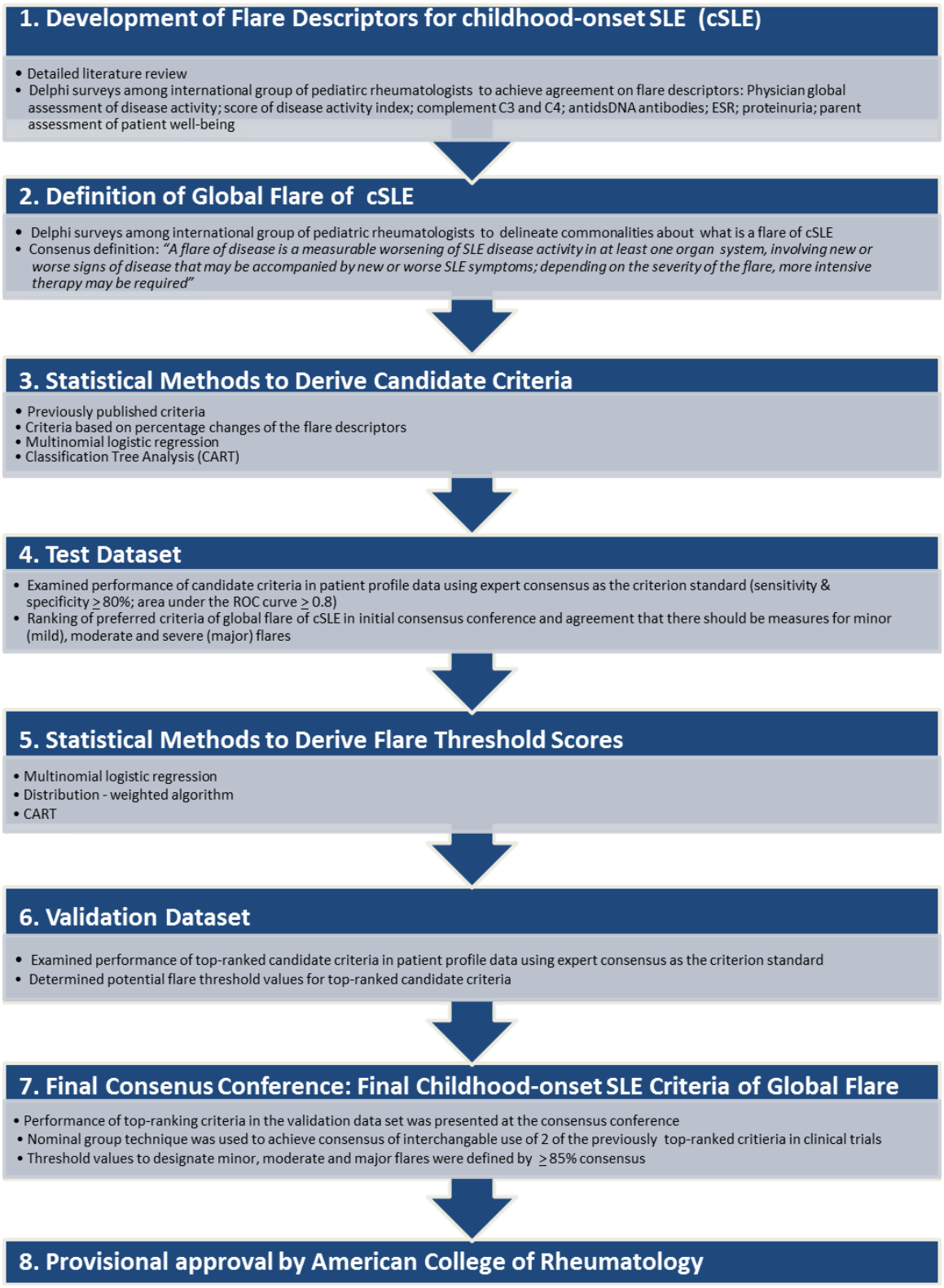
1. Development of Flare Descriptors for childhood-onset SLE (cSLE)
• Detailed literature review
• Delphi surveys among international group of pediatirc rheumatologists to achieve agreement on flare descriptors: Physician global assessment of disease activity; score of disease activity index; complement C3 and C4; antidsDNA antibodies; ESR; proteinuria; parent assessment of patient well-being
2. Definition of Global Flare of cSLE
• Delphi surveys among international group of pediatric rheumatologists to delineate commonalities about what is a flare of cSLE
• Consenus definition: "A flare of disease is a measurable worsening of SLE disease activity in at least one organ system, involving new or worse signs of disease that may be accompanied by new or worse SLE symptoms; depending on the severity of the flare, more intensive therapy may be required"
3. Statistical Methods to Derive Candidate Criteria
• Previously published criteria
• Criteria based on percentage changes of the flare descriptors
• Multinomial logistic regression
• Classification Tree Analysis (CART)
4. Test Dataset
• Examined performance of candidate criteria in patient profile data using expert consensus as the criterion standard (sensitivity & specificity ≥ 80%; area under the ROC curve ≥ 0.8)
• Ranking of preferred criteria of global flare of cSLE in initial consensus conference and agreement that there should be measures for minor (mild), moderate and severe (major) flares
5. Statistical Methods to Derive Flare Threshold Scores
• Multinomial logistic regression
• Distribution - weighted algorithm
• CART
6. Validation Dataset
• Examined performance of top-ranked candidate criteria in patient profile data using expert consensus as the criterion standard
• Determined potential flare threshold values for top-ranked candidate criteria
7. Final Consenus Conference: Final Childhood-onset SLE Criteria of Global Flare
• Performance of top-ranking criteria in the validation data set was presented at the consensus conference
• Nominal group technique was used to achieve consensus of interchangable use of 2 of the previously top-ranked critieria in clinical trials
• Threshold values to designate minor, moderate and major flares were defined by ≥ 85% consensus
8. Provisional approval by American College of Rheumatology

Figure 1. Flow diagram of the entire process used to develop and validate the approved criteria of global flare of cSLE. Steps 1–5 have been summarized in references 5 and 14. The current study begins at step 5 and focuses on steps 6–8. antidsDNA = anti–double-stranded DNA; ESR = erythrocyte sedimentation rate; ROC = receiver operating characteristic curve.

and score = 1 if otherwise). Similar to algorithms derived by multinomial logistic regression, CART-based criteria yield "CART-scores" that can be used to decide on the presence of a flare, including its severity (14).

Step A: PPs and ratings of disease course of a PP. Two of the authors (HIB and MH) conducted a pilot study to test the format of the PP. Built on this pilot study, we generated over 2,996 unique PPs, using prospectively collected data of cSLE patients from the Cincinnati Children's Hospital Medical Center Lupus Registry (18), the Paediatric Rheumatology International Trials Organisation Lupus Cohort (19), the UK Juvenile-Onset SLE Cohort Study (20), and the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial (21). Missing observations in the data sets were imputed using multiple imputation methods and expectation–maximization algorithms in computation (22–24).

Each PP provided data about a patient at the time of a baseline visit and a followup visit. For each PP visit, the cSLE flare descriptors were provided (5) as follows: 1) MD-global, measured on a visual analog scale (VAS; 0 = inactive disease, 10 = very active disease); 2) parent assessment of patient overall well-being, measured on a VAS with a range from 0 to 10 (0 = very poor, 10 = very well); 3) proteinuria, measured by timed urine collection or spot PCR; 4) ESR; 5) levels of complement C3 and C4; and 6) item and summary scores of the SLEDAI-2K (7), or the domain and summary scores of the BILAG using the following numeric conversion: A = 12, B = 8, C = 1, and D/E = 0 (8). Information on complete blood counts and differential, serum chemistry, urinalysis, and anti–double-stranded DNA antibodies were also provided. Details on PP formats for the SLEDAI and BILAG are provided in Supplementary Appendices A and B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23557/abstract.

PP raters were randomly assigned to assess the disease course of a maximum of 51 PPs. Response options offered were major flare, moderate flare, minor flare, unchanged, improved, or "I do not have enough information to make this assessment." A global flare was considered as "present" whenever the disease course was rated as minor, moderate, or major flare.

Step B: adjudication of disease course of the PP. A randomization scheme was preplanned to ensure that each PP was sent to about 13 raters, with the ratio of American and international raters matching that of the PP raters' pool (about 1:1). PPs with fewer than 4 ratings were regarded as "invalid" or "unqualified" and excluded from further consideration. Only "qualified" PPs with successful adjudication were considered in step 3.

Given that PP raters may not necessarily agree on the disease course, the "true" overall course of cSLE for a given PP was adjudicated using 2 approaches: 1) 67% rule: at least two-thirds of the raters agreed on a given disease course, and 2) majority-rule: the majority of the raters of a PP agreed on a given disease course. Other rules (50% rule and 75% rule) were also explored, and results were similar to the majority-rule and the 67% rule, respectively; therefore, they are not presented herein.

Step C: assessment of performance. *Statistical analysis in preparation of the testing of preliminary flare criteria.* Considering the intended widespread use of the cSLE flare criteria (14), we tested whether there were systematic differences in the ratings provided by raters from 1) different geographic regions or 2) with varying professional experience as measured by the duration of medical practice. Agreement among raters was assessed using intraclass correlation coefficients (ICCs) and/or kappa (κ) statistics. An ICC or a kappa value can be interpreted as follows: poor agreement: ICC or $\kappa < 0.4$, fair to good agreement: ICC or $\kappa \geq 0.4$–0.75, and substantial to excellent agreement: ICC or $\kappa > 0.75$ (25).

Performance and accuracy. Each of the 4 flare algorithms (SLEDAI-based criteria, BILAG-based criteria, SLEDAI-CART, and BILAG-CART) was assessed for diagnostic accuracy using receiver operating characteristic (ROC) curve analysis. Specifically, the area under the ROC curve (AUC) was calculated, and the diagnostic accuracy was considered outstanding, excellent, good, fair, and poor if the AUC was in the range of 0.9–1.0, 0.81–0.90, 0.71–0.80, 0.61–0.70, and <0.60, respectively (14,26). In contrast to the flare criteria derived from multinomial regression models (SLEDAI- and BILAG-based criteria), CART-based flare algorithms (SLEDAI-CART and BILAG-CART) result in a single discrete value for sensitivity and specificity, respectively. Considering all possible flare scores, the overall diagnostic accuracy of an algorithm can be estimated.

Threshold score candidates for algorithms derived by multinomial logistic analysis. In the absence of strong guidance from the ACR, we used 2 statistical methods to define potential threshold scores. First, in an earlier phase of the project, consensus had been achieved that "flare score threshold" for a given algorithm should reflect the highest conditional AUC among all candidate thresholds on a ROC curve. Hence, these flare score thresholds represent the point on the ROC curves with the highest precision of correctly classifying the severity of a cSLE flare. Second, we also explored a distribution-weighted approach in which the flare score threshold was calculated based upon the average of means of scores in 2 neighboring flare states weighted by the SDs of the scores. The performance of the candidate thresholds from both statistical analyses described above was calculated, as well as average accuracies for the correct identification of minor, moderate, and major flares for the SLEDAI-based and BILAG-based algorithms.

Step D: ranking of candidate flare criteria and thresholds score. To support decision making, consensus conference participants reviewed a syllabus that provided the results of the preceding Delphi surveys, relevant published medical literature, and the results of the statistical analyses prior to the consensus conference (see step 3). Participants in the consensus conference were 13 experienced pediatric rheumatologists and nephrologists from South America, North America, Asia, and Europe with substantial clinical and research experience in cSLE (HIB, MWB, SPA, SA, CAS, FF, BG, SEW, DML, AR, RK, TA, and MKG).

A priori, the consensus level at the consensus conference was set at 75%, i.e., comparable or even somewhat higher than that chosen for similar studies in the past (15–18).

Using nominal group technique guided by an experienced moderator (BMF), the expert panel assessed each of the 4 top candidate flare algorithms (14) and potential flare score thresholds according to 1) feasibility (i.e., practicability: can the items be measured easily?), 2) reliability (i.e., reproducibility: can the items be measured precisely?), 3) redundancy (are there 2 or more items included in the candidate criteria measuring the same aspect of the disease?), 4) face validity (i.e., credibility: are the criteria sensible?), 5) content validity (i.e., comprehensiveness: do the criteria sample all of the domains of the disease?), 6) criterion validity: based on AUC, do the criteria accurately approximate the gold standard? (i.e., the adjudicated disease course as per the 67% rule or majority-rule), 7) sensitivity and specificity (do the criteria effectively identify patients with cSLE flares and distinguish them from patients who do not have a flare of their cSLE?), and 8) discriminant validity: do the criteria detect the smallest clinically important change? (i.e., discriminate patients with 1 of the following disease courses: minor flare, moderate flare, major flare, or no flare). Based on the above considerations, the consensus conference experts were asked to rank the candidate flare criteria from 1 (lowest criterion) to 4 (highest criterion).

The survey source data were batch processed, and open-source online survey software, LimeSurvey, was used for response management and as a presentation layer (see http://www.limesurvey.org/). All analyses were done using SAS, version 9.4, software and SYSTAT 12 software. *P* values less than 0.05 were considered statistically significant.

Table 1. Baseline characteristics of validation cohort*

	Majority rule (n = 1,860)	67% rule (n = 818)
Mean age, years	15.0	15.1
Female sex, %	81.7	82.5
Protein-creatinine ratio†	0.39	
≤0.2	63.8	67.5
>0.2	36.2	32.5
>0.5	14.5	13.0
>2.0	3.4	2.7
Organ involvement with active cSLE at baseline		
Neuropsychiatric	2.7	7.0
Musculoskeletal	12.4	8.67
Mucocutaneous	21.7	22.6
Hematologic	15.4	12.7
Renal	24.1	20.5
Cardiopulmonary	1.2	1.0
Constitutional symptoms	2.7	8.1

* Values are the percentage of the number, unless indicated otherwise. cSLE = childhood-onset systemic lupus erythematosus.
† Either from 24-hour urine or random urine sample (mg protein/mg urine creatinine).

Ethics review. The study was approved by the institutional review boards of the participating pediatric rheumatology centers. Informed consent was obtained from all parents and, as appropriate, participants assented prior to the study procedures.

Table 2. Change of descriptors in relationship to cSLE disease course*

Flare descriptor/rule	(1) Improved/ no change	(2) Minor flare	(3) Moderate flare	(4) Major flare	(1) vs. (2), adjusted *P*	(2) vs. (3), adjusted *P*	(3) vs. (4), adjusted *P*
ESR							
Majority	−0.02 ± 1.30	8.81 ± 1.34	22.80 ± 1.38	28.99 ± 1.68	< 0.0001	< 0.0001	0.023
67%	0.54 ± 1.58	7.28 ± 2.07	31.95 ± 2.39	35.34 ± 2.41	0.048	0.000	0.749
MD-global							
Majority	0.66 ± 0.50	3.05 ± 0.52	5.92 ± 0.53	7.95 ± 0.65	0.005	0.001	0.075
67%	0.76 ± 0.60	2.70 ± 0.79	7.74 ± 0.91	9.79 ± 0.92	0.210	< 0.0001	0.392
Protein-creatinine ratio							
Majority	0.02 ± 0.07	0.10 ± 0.07	0.66 ± 0.07	1.44 ± 0.08	0.843	< 0.0001	< 0.0001
67%	0.03 ± 0.07	0.02 ± 0.09	0.64 ± 0.11	1.61 ± 0.11	1.000	< 0.0001	< 0.0001
SLEDAI							
Majority	1.81 ± 0.26	4.58 ± 0.28	8.45 ± 0.29	16.00 ± 0.36	0.000	< 0.0001	< 0.0001
67%	1.56 ± 0.35	4.63 ± 0.48	9.98 ± 0.56	19.88 ± 0.55	0.000	< 0.0001	< 0.0001
BILAG							
Majority	3.12 ± 1.08	7.76 ± 0.93	15.19 ± 0.95	24.19 ± 1.15	0.007	< 0.0001	< 0.0001
67%	1.79 ± 1.34	8.63 ± 1.50	15.64 ± 1.61	28.71 ± 1.75	0.005	0.010	< 0.0001
SLEDAI-based flare algorithm							
Majority	−0.23 ± 0.17	1.66 ± 0.18	4.79 ± 0.19	9.88 ± 0.23	< 0.0001	< 0.0001	< 0.0001
67%	−0.34 ± 0.21	1.67 ± 0.29	5.84 ± 0.34	12.34 ± 0.34	< 0.0001	< 0.0001	< 0.0001
BILAG-based flare algorithm							
Majority	0.40 ± 0.56	3.00 ± 0.48	7.10 ± 0.49	11.96 ± 0.60	0.003	< 0.0001	< 0.0001
67%	−0.11 ± 0.66	3.49 ± 0.76	8.23 ± 0.79	15.05 ± 0.88	0.003	< 0.0001	< 0.0001

* Values presented are changes in means ± SDs, adjusted for multiple comparisons using the Tukey's method, unless indicated otherwise. cSLE = childhood-onset systemic lupus erythematosus; ESR = erythrocyte sedimentation rate; MD-global = physician global assessment of disease activity; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; BILAG = British Isles Lupus Assessment Group.

RESULTS

PP raters and validation data set (steps A and 2). A total of 2,996 ratings were provided to 503 pediatric rheumatologists and used for step 2. The response rate of the pediatric rheumatologists to the PP was 54% (274 of 503; locations: 30% from the US and Canada, 8% from Australia/Asia, 3% Africa/Middle East, 40% South and Central America, and 19% from Europe). The majority (69%) of PP raters had over 10 years of experience in treating cSLE. There were 1,860 PPs (1,860 of 2,996 [62%]) that were rated by at least 4 raters and therefore considered "qualified" for inclusion in step 3. There were no significant differences of distribution of flares between qualified and unqualified PPs ($P = 0.62$ by Fisher's exact test).

When the majority rule was applied to the "qualified" PPs, there were 1,318 PPs representing global flares (510 minor flares, 483 moderate flares, and 325 major flares) and 542 unchanged/improved (29% of 1,860 PPs). When applying the 67% rule to the 1,860, only 818 PPs remained available for analysis, among them 484 representing a flare (194 minor flares, 146 moderate flares, and 144 major flares) and 334 PPs without cSLE flare. The patient characteristics reflected in these PPs are summarized in Table 1. PP raters from different geographic locations did not differ systematically in the disease course assignment for a given PP (North America versus other countries: ICC 0.658). Similarly, there was fair to good agreement among PP raters with different duration of medical experience (3–5, 6–10, 10–15, and >15 years) for the interpretation of the disease courses (ICC 0.656). Additionally, we explored other selection criteria (50% rule, 75% rule) and found no systematic differences with the 50% rule and 75% rule, resulting in similar adjudication of the PP compared to the majority-rule and the 67% rule, respectively (data not shown).

Performance of preliminary algorithms of cSLE global flares (step C). The absolute baseline-to-followup changes of the parameters considered in the preliminary flare algorithms by flare severity and rule are provided in Table 2. Irrespective of the data set (67% rule, majority-rule), most of the cSLE flare descriptors included in the preliminary cSLE flare criteria (ESR, PCR, MD-global, SLEDAI, and BILAG) significantly changed between the baseline and followup visit, by flare severity. Notably, the accuracy of the SLEDAI-based algorithm was outstanding (AUC 0.93, 95% confidence interval [95% CI] 0.91–0.95), as was that of the BILAG-based algorithm (AUC 0.93, 95% CI 0.89–0.98). The CART-SLEDAI algorithm had an excellent accuracy for identifying patients with global flare of cSLE (any severity) (AUC 0.89, sensitivity 88.8%, and specificity 87.1%). The same was true for the CART-BILAG criteria (AUC 0.84, sensitivity 93.9%, and specificity 72.9%). Comparisons of accuracies in the development data set in 2010 (18) and this validation data set are summarized in Table 3.

Figure 2A and B depict potential thresholds for defining minor, moderate, and major flares. In this final consensus conference, again consensus (100%) was reached to use the statistically optimal threshold from logistic models to define all threshold scores for the both SLEDAI-based and the BILAG-based algorithms. As shown in Figure 3A and B, using these threshold cutoff scores allows for the discrimination of minor from moderate or severe flares, all with sensitivities and specificities of ≥82%. Neither of the CART-based algorithms was suited

Table 3. Comparison of the performance of the preliminary flare algorithm in the development and validation data set*

			AUC	
	Algorithm	Flare category	2010 data	2017 data
SLEDAI-based flare score†	Score = 0.5 × SLEDAI + 0.45 × PCR + 0.5 × MD + 0.02 ESR	Major flare	0.95	0.93
		At least moderate flare	0.85	0.94
		At least minor flare	0.86	0.93
BILAG-based flare score†	Score = 0.4 × BILAG + 0.65 × PCR + 0.5 × MD + 0.02 ESR	Major flare	0.93	0.91
		At least moderate flare	0.85	0.92
		At least minor flare	0.85	0.93
SLEDAI-based CART rule	Score = 4 if 3 ≤ SLEDAI	Major flare	0.85	0.76
	Score = 3 if 0.7 ≤ PCR and 3 > SLEDAI	At least moderate flare	0.80	0.80
	Score = 2 if 2 ≤ MD and 0.7 > PCR and 3 > SLEDAI	At least minor flare	0.84	0.89
	Score = 1 if otherwise			
BILAG-based CART rule	Score = 4 if 2 ≤ BILAG	Major flare	0.86	0.71
	Score = 3 if 0.7 ≤ PCR and 2 > BILAG	At least moderate flare	0.80	0.75
	Score = 2 if 2 ≤ MD and 0.7 > PCR and 2 > BILAG	At least minor flare	0.82	0.84
	Score = 1 if otherwise			

* Values presented represent the area under the receiver operating characteristic curve (AUC) considering patient profile (PP) with consensus as defined by the 67% rule. Numeric values larger than or equal to the flare score signify a flare; higher scores are seen with more severe flare. See reference 14 for details about algorithm development. SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; PCR = urine protein/creatinine ratio from random urine sample; MD = physician global assessment of disease measured on a visual analog scale (range 0–10, where 0 = inactive disease); ESR = erythrocyte sedimentation rate; BILAG = British Isles Lupus Assessment Group; CART = classification tree analysis.
† Algorithm considers for the change (baseline – followup) of each of the flare descriptors included.

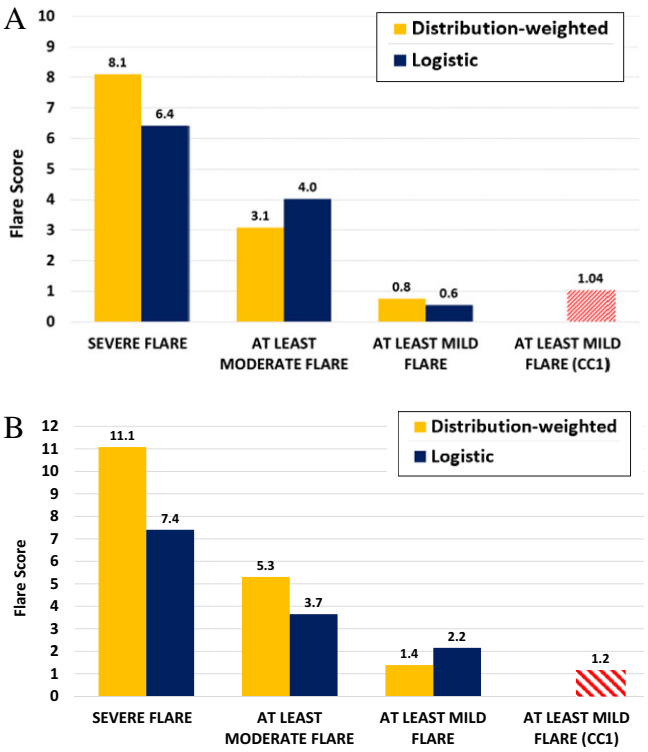

Figure 2. Potential flare thresholds to define childhood-onset systemic lupus erythematosus flare severity. **A**, Systemic Lupus Erythematosus Disease Activity Index–based algorithm, **B**, British Isles Lupus Assessment Group–based algorithm. Flare threshold values based on multinomial logistic regression models (blue bars) and distribution-weighted strategies (yellow bars) for each flare category (minor, moderate, major flare) were presented to the experts participating in the final consensus conference. There was 100% agreement to use threshold values derived from multinomial logistic regression, i.e., thresholds with the best statistical performance in receiver operating characteristic (ROC) curve analysis. Each threshold had the largest summation of sensitivity and specificity on the ROC curve. Red bars indicate the scores using each algorithm to assess the 2010 data (14). CC1 = Threshold value for flare as agreed upon in the initial consensus conference (see Step 4, Figure 1).

to discriminate between mild and moderate cSLE flares (Figure 3C and D).

Ranking of the preliminary cSLE flare algorithms (step D). Consensus conference participants achieved consensus that the BILAG-based (92%) and SLEDAI-based (100%) flare algorithms both have construct validity for measuring global flares of cSLE. There was consensus (100%) to recommend that both measures be collected in future cSLE clinical trials and that either one may be chosen as the primary end point. Consistent with their performance in the validation data set, no consensus was reached whether one of these 2 algorithms was preferable to the other. Consensus was achieved that CART-based algorithms are not suited for use in clinical trials, given that these algorithms cannot be used to discriminate minor from moderate cSLE flares. The results of this study were reviewed by the ACR Criteria Subcommittee and the ACR Quality of Care Committee.

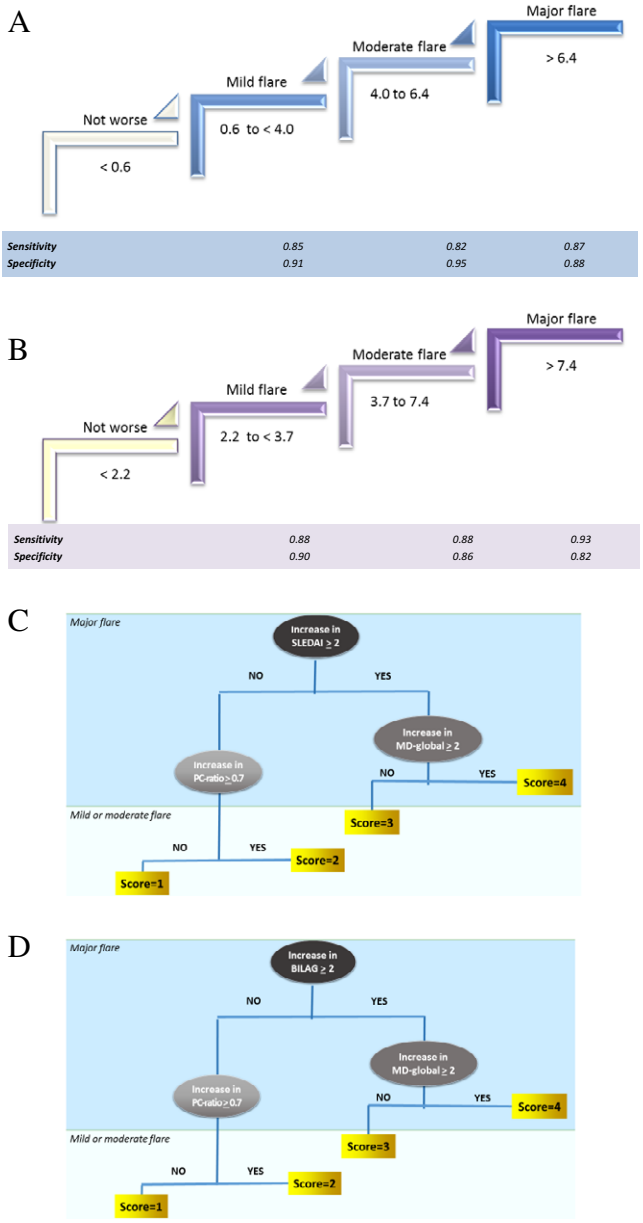

Figure 3. Flare score interpretation. Flare scores represent the cutoff score on the receiver operating characteristic curves that provide the best discrimination between adjacent disease states (no flare, minor or mild flare, moderate flare, major or severe flare) with childhood-onset systemic lupus erythematosus (cSLE). Sensitivities and specificities are shown for the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)–based algorithm (**A**) and the British Isles Lupus Assessment Group (BILAG)–based algorithm (**B**). The SLEDAI–classification tree analysis (CART) algorithm (**C**) (where score = 4 if 3 ≤ SLEDAI, score = 3 if 0.7 ≤ protein/creatinine ratio [PC-ratio] and 3 > SLEDAI, score = 2 if 2 ≤ physician global assessment [MD-global] and 0.7 > PC-ratio and 3 > SLEDAI, and score = 1 if otherwise) and in the BILAG-CART algorithm (**D**) (where score = 4 if 2 ≤ BILAG, score = 3 if 0.7 ≤ PC-ratio and 2 > BILAG, score = 2 if 2 ≤ MD-global and 0.7 > PC-ratio and 2 > BILAG, and score = 1 if otherwise) are only able to distinguish major flares from other cSLE disease courses. Thus, the other 2 of the top preliminary flare criteria (SLEDAI-CART, BILAG-CART) were unable to discriminate minor from moderate cSLE flare.

DISCUSSION

The need to develop internationally agreed upon criteria for disease flares has become more urgent since the introduction of randomized withdrawal trials in pediatric rheumatology, in which time to flare or the proportion of patients who experience a flare are used as primary efficacy measures (27). We confirm the outstanding accuracy of the previously developed preliminary criteria of global flares of cSLE, based on large international data sets used for validation. Consensus has been achieved on how to interpret flare scores. The preferred cSLE global flare algorithms for use in clinical trials were derived from multinomial logistic regression models. These algorithms consider the differential and complementary contribution of select cSLE flare descriptors in identifying disease flares in this disease with highly variable multiorgan involvement. Despite consensus that CART-based algorithms are potentially of value when used in clinical care settings, there was agreement that they should not be used in clinical trials. As for SLE in adulthood, measures of the overall course are especially relevant because not all cSLE features improve or worsen in parallel. Current drugs used in cSLE therapy are not equally effective in reducing disease activity in the various organ systems. Thus, it is reasonable to assume that the same holds true for new or emerging drugs for cSLE. In clinical trials aimed at reducing cSLE-mediated inflammation in certain organ systems, it appears mandatory to ensure that global disease, i.e., disease manifestations in other than the target organ systems, is not worsening. The results of this study support that the SLEDAI-based and the BILAG-based flare scores are both highly suited to provide such information.

Based on the current evidence about these algorithms, they are similarly sensitive, specific, and accurate. Hence, consensus conference experts considered both algorithms equally valuable and suitable for use in clinical trials. Different from what is currently used to gauge response to therapy in juvenile idiopathic arthritis (11), flare algorithms derived from regression models allow for consideration of the differential importance of changes in individual cSLE flare descriptors when recognizing cSLE flares. The SLEDAI-based and BILAG-based flare scores are reminiscent of the Disease Activity Score (DAS) used in rheumatoid arthritis (28). However, the DAS considers the natural logarithm of the ESR and square roots of the number of swollen or tender joints, while the preliminary cSLE flare criteria require at most simple arithmetic maneuvers to calculate a cSLE flare score, supporting their ease of use (14).

All flare score algorithms consider changes in proteinuria, despite the inclusion of proteinuria assessment in the SLEDAI and BILAG scores. This allows for detection of renal SLE flares that occur in patients with existing proteinuria and also allows for the consideration of increases in proteinuria that would otherwise not be captured given the item definition used in the SLEDAI and BILAG, respectively. As reported previously, exclusion of changes in proteinuria from the flare algorithms resulted in inferior accuracy in predicting cSLE flares (14).

In line with our earlier studies (5,8), both cSLE flare criteria from CART and multinomial logistic regression analysis showed excellent or even outstanding accuracy. Statistically, they were superior to algorithms that considered equally weighted percentage changes from a statistical point of view in the past.

Given the simplicity of CART-based criteria, they appear particularly suited for clinical settings, but a potential shortcoming of CART-based criteria includes so-called "over-fitting of the mathematical model," which can make them prone to less favorable statistical performance in subsequent validation studies (14). Mild cSLE flares often do not prompt clinicians to change therapy, whereas moderate cSLE flares generally require more intensive antiinflammatory therapy. Although CART-based flare algorithms were highly accurate for discriminating any kind of global flare when tested in this validation data set, they were unable to distinguish minor from moderate cSLE flares. This limitation prompted the agreement among the consensus conference experts to not recommend CART-based algorithms for use as outcome measures in clinical trials.

We chose 2 approaches to adjudicate the disease course (67% rule, majority rule) presented in the various PPs, which might have introduced bias. However, both approaches yielded comparable results.

The ACR has outlined a series of validation steps necessary before new criteria are to be widely used for clinical care or research (12). Among others, one step is to use data from clinical trials for developing response criteria. However, clinical trial data from interventions that impact cSLE activity are unavailable at present. In our study, the presence of a flare was based on the PP raters' perception of the course of cSLE instead. Given their prospective character and the expertise of the PP raters, we consider the quality of our data to be high, and the number of PPs per flare severity category yielded robust provisional cSLE flare criteria.

We would like to point out that PP raters from different parts of the world and different degrees of experience all showed excellent concordance (interrater agreement) in their assessment of the cSLE course. This supports the robustness of this validation study. A limitation might be that only 54% of those physicians approached to provide PP ratings provided feedback. Nonetheless, responses from 274 pediatric rheumatologists were obtained, which is a much larger number than for many similar validation exercises (9–11).

In addition to criteria for global flare and improvement, criteria for changes of cSLE in specific organ systems are likely needed. Depending on the proposed effect of a cSLE drug candidate, the Cutaneous Lupus Activity and Severity Index (29), pediatric lupus nephritis response measures (30), and standardized joint assessments for children (11) have already been validated to adequately capture the proposed therapeutic effects. To further provide support for the accuracy of the provisional criteria of global flare of cSLE, data from clinical trials will be needed.

Taken together, a methodologically stringent validation process has been employed to calculate a flare score that can be used to interpret the course of cSLE over time with respect to the degree of worsening that might have occurred. Based on the data available, these algorithms cannot be used to quantify potential improvement over time.

ACKNOWLEDGMENTS

We thank Kasha Wiley (overall study coordination), Susan Priest (consensus conference logistics), Pinar Avar (consensus conference support and data management), and Carly Muller, Malea Rolfsen, Allen Watts, Gaurav Gulati, and Jamie Meyers-Eaton (patient profile testing) from Cincinnati Children's Hospital Medical Center (CCHMC), as well as CCHMC Biomedical Informatics (web-based data management application development). We also thank Drs. Laura Schanberg and Christy Sandberg and the Childhood Arthritis and Rheumatology Research Alliance for provision of the data from the Atherosclerosis Prevention in Pediatric Lupus Erythematosus clinical trial, as well as the UK Juvenile-Onset SLE (JSLE) Study Group, for provision of the data from the UK JSLE Cohort Study. We are indebted to the members of the External Scientific Advisory Committee of this study for their advice in the study implementation, conduction, and its statistical analysis: Drs. Tuhina Neogi, Ian Bruce, David Isenberg, Nicola Ruperto, and James Witter. For a list of physicians who made important contributions to this work by providing their expertise when rating the patient profiles, see Supplementary Appendix C, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23557/abstract.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Brunner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Brunner, Holland, Beresford, Ardoin, Appenzeller, Silva, Flores, Goilav, Wenderfer, Levy, Ravelli, Khunchandani, Avcin, Klein-Gitelman, Feldman, Ruperto, Ying.

Acquisition of data. Brunner, Holland, Beresford, Ardoin, Appenzeller, Silva, Flores, Goilav, Wenderfer, Levy, Ravelli, Khunchandani, Avcin, Klein-Gitelman, Feldman, Ruperto, Ying.

Analysis and interpretation of data. Brunner, Holland, Beresford, Ardoin, Appenzeller, Silva, Flores, Goilav, Wenderfer, Levy, Ravelli, Khunchandani, Avcin, Klein-Gitelman, Feldman, Ruperto, Ying.

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Arthritis & Rheumatology
Vol. 74, No. 4, April 2022, pp 570–585
DOI 10.1002/art.42036
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2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for Nonpharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging

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Objective. To provide recommendations for the management of juvenile idiopathic arthritis (JIA) with a focus on nonpharmacologic therapies, medication monitoring, immunizations, and imaging, irrespective of JIA phenotype.

Methods. We developed clinically relevant Patient/Population, Intervention, Comparison, and Outcomes questions. After conducting a systematic literature review, the Grading of Recommendations Assessment, Development and Evaluation approach was used to rate the quality of evidence (high, moderate, low, or very low). A Voting Panel including clinicians and patients/caregivers achieved consensus on the direction (for or against) and strength (strong or conditional) of recommendations.

Results. Recommendations in this guideline include the use of physical therapy and occupational therapy interventions; a healthy, well-balanced, age-appropriate diet; specific laboratory monitoring for medications; widespread use of immunizations; and shared decision-making with patients/caregivers. Disease management for all patients with JIA is addressed with respect to nonpharmacologic therapies, medication monitoring, immunizations, and imaging. Evidence for all recommendations was graded as low or very low in quality. For that reason, more than half of the recommendations are conditional.

Conclusion. This clinical practice guideline complements the 2019 American College of Rheumatology JIA and uveitis guidelines, which addressed polyarthritis, sacroiliitis, enthesitis, and uveitis, and a concurrent 2021 guideline

on oligoarthritis, temporomandibular arthritis, and systemic JIA. It serves as a tool to support clinicians, patients, and caregivers in decision-making. The recommendations take into consideration the severity of both articular and nonarticular manifestations as well as patient quality of life. Although evidence is generally low quality and many recommendations are conditional, the inclusion of caregivers and patients in the decision-making process strengthens the relevance and applicability of the guideline. It is important to remember that these are recommendations. Clinical decisions, as always, should be made by the treating clinician and patient/caregiver.

INTRODUCTION

Reflecting the changing medical landscape, the American College of Rheumatology (ACR) regularly updates clinical practice guidelines and plans to review these annually and update as needed. The process for updating the 2011 and 2013 juvenile idiopathic arthritis (JIA) guidelines (1,2) began in 2017. Important clinical topics for consideration were first identified at a meeting to define the scope of the guidelines. Advances in the treatment of JIA and better understanding of pathogenesis dictated separating this clinical practice guideline into several parts due to the breadth of topics. The first part, addressing polyarthritis, sacroiliitis, enthesitis, and uveitis, was published in 2 articles in 2019 (3,4). The second part, presented here in 2 articles, covers 1) oligoarthritis, temporomandibular joint (TMJ) arthritis, and systemic JIA, and 2) nonpharmacologic treatments, patient monitoring, immunizations, and imaging (5). The methods and literature review described below reflect the unified process used for the second part of these guidelines, including both articles.

We developed clinically relevant Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions. Using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, recommendations were then developed based on the best available evidence for commonly encountered clinical scenarios. Prior to final voting, input was sought from relevant stakeholders including a panel of young adults with JIA and caregivers of children with JIA to consider their values and perspectives in making recommendations. Both the patient/caregiver and guideline Voting Panels stressed the need for individualized treatment while being mindful of available evidence and the need to include recommendations on nonpharmacologic therapies.

METHODS

This guideline followed the ACR guideline development process and ACR policy guiding management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), which include GRADE methodology (6,7), and adheres to Appraisal of Guidelines, Research and Evaluation criteria (8). Supplementary Appendix 1 (available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42036/abstract) includes a detailed description of the methods. Briefly, the Core Leadership Team (KBO, DBH, DJL, SS) drafted clinical PICO questions. PICO questions were revised and finalized based on feedback from the entire guideline development group and the public. The Literature Review Team performed systematic literature reviews for each PICO (for search terms, see Supplementary Appendix 2,

This article is published simultaneously in *Arthritis Care & Research*.

Supported by the American College of Rheumatology. Dr. Horton's work was supported by funding from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (award K23-AR-070286). Dr. Ombrello's work was supported by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (award AR-041198).

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.42036&file=art42036-sup-0001-Disclosureform.pdf.

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Submitted for publication March 4, 2021; accepted in revised form November 23, 2021.

https://onlinelibrary.wiley.com/doi/10.1002/art.42036/abstract), graded the quality of evidence (high, moderate, low, or very low), and produced the evidence report (Supplementary Appendix 3, https://onlinelibrary.wiley.com/doi/10.1002/art.42036/abstract). It should be noted that GRADE methodology does not distinguish between lack of evidence (i.e., none) and very low–quality evidence. The Core Team defined multiple critical study outcome(s) for PICOs relevant to each JIA phenotype (Supplementary Appendix 4, https://onlinelibrary.wiley.com/doi/10.1002/art.42036/abstract).

A panel of 15 members, including young adults with JIA and caregivers of children with JIA, met virtually (moderated by the principal investigator [KBO]), reviewed the evidence report, and provided input to the Voting Panel. Two members of this panel were also members of the Voting Panel to ensure that the patient voice was part of the entire process. The Voting Panel reviewed the evidence report and patient/caregiver perspectives and then discussed and voted on recommendation statements. Consensus required ≥70% agreement on both direction (for or against) and strength (strong or conditional) of each recommendation, as per ACR practice. A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when the decision is sensitive to individual patient preferences, or when costs are expected to impact the decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision-making. Examples of each class of intervention addressed in the recommendations are shown in Table 1. Rosters of the Core Leadership Team, Literature Review Team, and both panels are included in Supplementary Appendix 5 (https://onlinelibrary.wiley.com/doi/10.1002/art.42036/abstract).

Table 1. Classes of interventions

Nonsteroidal antiinflammatory drugs	Any at therapeutic dosing (ibuprofen, naproxen, tolmetin, indomethacin, meloxicam, nabumetone, diclofenac, piroxicam, etodolac, celecoxib)
Conventional synthetic disease-modifying antirheumatic drugs	Methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, calcineurin inhibitors (cyclosporin A, tacrolimus)
Biologic disease-modifying antirheumatic drugs	Tumor necrosis factor inhibitors (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol); other biologic response modifiers (abatacept, tocilizumab, anakinra, canakinumab)
Targeted synthetic disease-modifying antirheumatic drugs	JAK inhibitor (tofacitinib)
Glucocorticoids	Oral (any); intravenous (any); intraarticular (triamcinolone acetonide, triamcinolone hexacetonide)
Immunizations	Live attenuated; inactivated
Nonpharmacologic therapies	Physical therapy; occupational therapy; dietary changes; herbal supplements

Guiding principles

The development of the recommendations presented herein was guided by the following principles:

1. Consistent with the ACR's 2019 JIA guidelines, these recommendations are for persons already diagnosed as having JIA.
2. Coexisting extraarticular conditions that would influence disease management and monitoring, such as uveitis, psoriasis, or inflammatory bowel disease, are not addressed within these guidelines.
3. Recommendations for immunizations were evaluated to be consistent with guidelines from the American Academy of Pediatrics (AAP) and the Advisory Committee on Immunization Practices (ACIP) while taking into consideration the unique needs of persons with JIA.
4. Recommendations are intended to be used by all clinicians caring for persons with JIA.
5. Shared decision-making with families and patients is critical.

RESULTS/RECOMMENDATIONS

The initial literature review (through August 7, 2019) identified 4,308 articles in searches for all PICO questions pertaining to oligoarthritis, TMJ arthritis, systemic JIA, and the topics addressed in this report, including nonpharmacologic therapies, nutrition, supplements, medication monitoring, immunizations, and imaging. A July 9, 2020 search update identified 367 more references, for a total of 4,675 articles after duplicates and non-English publications were removed. After exclusion of 2,291 titles and abstracts, 2,384 full-text articles were screened. Of these, 1,939 were excluded (Supplementary Appendix 6, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42036/abstract), leaving 445 articles to be considered for the evidence report. Ultimately, 336 articles were matched to PICO questions and included in the final evidence report. Quality of evidence was uniformly low or very low; 17 PICO questions lacked any associated evidence and, as per GRADE methodology, were categorized as very low (Tables 2–6). The recommendations that follow are based on 62 PICO questions. Several PICO questions were split into 24 sub-PICO questions to

Table 2. Strength of recommendations and quality of supporting evidence

Topic	Strength of recommendation			Quality of supporting evidence			
	No. of recommendations	Conditional	Strong	Very low	Low	Moderate	High
Nonpharmacologic therapies	4	2	2	4	0	0	0
Medication monitoring*	20	17	3	17	0	0	0
Infection surveillance/immunizations	7	3	4	5	2	0	0
Imaging	2	1	1	2	0	0	0
Total	33	23	10	28	2	0	0

* Lack of evidence for tofacitinib given the US Food and Drug Administration approval date.

improve specificity. Nine questions initially posed were discarded by the Voting Panel because of redundancy or lack of relevance. Final recommendations are described below and in Tables 3–6, which include reference(s) to which PICO question(s) in the evidence report correspond to the recommendation statement.

Nonpharmacologic therapies (Table 3)

Patient/caregiver panelists specifically asked that recommendations for nonpharmacologic treatment be included in this guideline, although they understood that evidence to support specific statements is generally lacking.

Physical and occupational therapy (PT/OT)

PT and OT are conditionally recommended regardless of concomitant pharmacologic therapy.

Reasons for using PT or OT include maintaining or improving joint range of motion (particularly for contractures), improving strength, reversing functional deficits, improving endurance, preventing injury, and promoting improved participation in activities of daily living, family routines, and occupations (9,10).

Nutrition

A discussion of healthy, age-appropriate diet is strongly recommended.

Use of a specific diet to treat JIA is strongly recommended *against*.

Ample evidence supports the value of a healthy, balanced, nutrient-dense diet for all children, with consideration of specific age-appropriate nutritional requirements (e.g., fat, calcium)

Table 3. Nonpharmacologic therapies*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
A discussion of healthy, age-appropriate diet is **strongly** recommended.	Very low	PICO 7. In children with oligoarticular JIA, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are given, versus not recommending them?	48–49
Use of a specific diet to treat JIA is **strongly** recommended *against*.	Very low	PICO 7. In children with oligoarticular JIA, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are given, versus not recommending them?	48–49
Use of supplemental or herbal interventions specifically to treat JIA is **conditionally** recommended *against*.	Very low	PICO 17. In children with JIA with active TMJ arthritis, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are given, versus not recommending them?	60
Physical and occupational therapy are **conditionally** recommended regardless of concomitant pharmacologic therapy.	Very low	PICO 8. In children with oligoarticular JIA, regardless of disease activity and poor prognostic features, should PT/OT versus no PT/OT (regardless of concomitant medical therapy) be recommended?	49–51
		PICO 18. In children with JIA with active TMJ arthritis, regardless of disease activity and poor prognostic features, should PT versus no PT (regardless of concomitant medical therapy) be recommended?	60

* PICO = Patient/Population, Intervention, Comparison, and Outcomes; JIA = juvenile idiopathic arthritis; TMJ = temporomandibular joint; PT = physical therapy; OT = occupational therapy.
† In Supplementary Appendix 3, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42036/abstract.

Table 4. Medication monitoring*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
NSAIDs: Monitoring via CBC counts, LFTs, and renal function tests every 6–12 months is **conditionally** recommended.	Very low	PICO 30. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel, and urinalysis) for children receiving long-term daily NSAID treatment?	144–145
MTX: Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is **strongly** recommended.	Very low	PICO 31. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel) for children being treated with MTX (oral or subcutaneous)?	145–150
Decreasing the MTX dosage or withholding MTX is **conditionally** recommended if a clinically relevant elevation in LFT results or decreased neutrophil or platelet count is found.	Very low	PICO 32. After MTX (oral or subcutaneous) is initiated, is there a recommended medication change in response to elevated LFT results and decreased neutrophil or platelet count?	150–153
Use of folic/folinic acid in conjunction with MTX is **strongly** recommended.	Very low	PICO 7. In children with oligoarticular JIA, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are used, versus not recommending them?	60
SSZ: Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended.	Very low	PICO 33. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel) for children with JIA being treated with SSZ?	153–155
Decreasing the SSZ dosage or withholding SSZ is **conditionally** recommended if a clinically relevant elevation in LFT results or decreased neutrophil or platelet count is found.	Very low	PICO 34. After SSZ is initiated, is there a recommended medication change in response to elevated LFT results and decreased neutrophil or platelet count?	155–157
LEF: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3-4 months thereafter is **conditionally** recommended.	Very low	PICO 35. Should children with JIA receiving LEF have serum creatinine testing, urinalysis, CBC count, and LFTs before and during treatment, per manufacturer's recommendations?	157–158
Altering LEF administration is **conditionally** recommended if a clinically relevant elevation in LFT results occurs (temporary withholding of LEF if the ALT level is >3 times the upper limit of normal [ULN]), as per the package insert.	Very low	PICO 36. After LEF is initiated, should medication dosage be altered according to the package insert in response to elevated LFT results?	158–159
Baseline and annual retinal screening after starting HCQ are **conditionally** recommended.	Very low	PICO 37. Should children with JIA receiving treatment with HCQ have annual screening tests with automated visual fields, if age appropriate, plus spectral-domain optical coherence tomography, versus starting annual screening 5 years after treatment initiation?	159
HCQ: Monitoring via CBC counts and LFTs annually is **conditionally** recommended.	Very low	PICO 38. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel) for children with JIA being treated with HCQ?	159
TNFi: Monitoring via CBC counts and LFTs annually is **conditionally** recommended.	Very low	PICO 39. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel, and urinalysis) for children with JIA receiving TNFi treatment?	160–161
Abatacept: Doing no routine laboratory monitoring is **conditionally** recommended.	Very low	PICO 40. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel, and urinalysis) for children with JIA receiving abatacept treatment?	161–162
Tocilizumab: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended. Monitoring of lipid levels every 6 months is **conditionally** recommended, as per the package insert.	Very low	PICO 41. Should children with JIA receiving tocilizumab have serum creatinine testing, urinalysis, CBC count, and LFTs before and during treatment, per manufacturer's recommendations?	162

(Continued)

Table 4. (*Cont'd*)

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
Altering tocilizumab administration is **conditionally** recommended if monitoring reveals elevated LFT results (if 1–3 times the ULN, decrease the dosage or increase the interval between doses, if >3 times the ULN, withhold administration, if >5 times the ULN, discontinue treatment), neutropenia (500–1,000/mm^3), or thrombocytopenia (50,000–100,000/mm^3), as per the package insert.	Very low	PICO 42. After tocilizumab is initiated, should medication dosage be altered according to the package insert in response to elevated LFT results, neutropenia, and/or thrombocytopenia?	163
Anakinra: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended.	Very low	PICO 43. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel, and urinalysis) for children with JIA receiving anakinra treatment?	163–164
Canakinumab: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended.	Very low	PICO 44. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel, and urinalysis) for children with JIA receiving canakinumab treatment?	164
Tofacitinib: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended. Monitoring of lipid levels 1–2 months after starting treatment is **conditionally** recommended, as per the package insert. Altering tofacitinib administration is **strongly** recommended if monitoring reveals laboratory abnormalities of concern. Specifically, medication should be discontinued if the hemoglobin level is <8 gm/dl or decreases by >2 gm/dl, or for severe neutropenia (<500/mm^3) or lymphopenia (<500/mm^3), as per the package insert.	‡	‡	‡

* PICO = Patient/Population, Intervention, Comparison, and Outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; CBC = complete blood cell; LFTs = liver function tests; MTX = methotrexate; JIA = juvenile idiopathic arthritis; SSZ = sulfasalazine; LEF = leflunomide; ALT = alanine aminotransferase; ULN = upper limit of normal; HCQ = hydroxychloroquine; TNFi = tumor necrosis factor inhibitor.
† In Supplementary Appendix 3, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42036/abstract.
‡ Given recent approval for JIA and limited experience, recommendations are based on clinical trial, US Food and Drug Administration guidance, and evidence in adults.

(11,12). Therefore, it is worthwhile to address the importance of an age-appropriate diet (13). However, there is no evidence to date that supports the use of a specific diet alone to treat JIA (14,15). Furthermore, some overly restrictive diets (e.g., gluten-free, dairy-free) may result in nutritional deficits and risk of other harms (e.g., delay in treatment, cost, inconvenience).

Supplements

Use of supplemental or herbal interventions specifically to treat JIA is conditionally recommended *against*.

Voting panelists had concerns about the safety of unregulated supplements and herbal formulations and stressed the importance of discussion and transparency regarding their use. Some evidence of efficacy supports the use of supplements (e.g., fish oils) to treat joint inflammation in adults, but there are only very limited efficacy and safety data for JIA (16).

Monitoring

Medications (Tables 4 and 5)

When making decisions regarding laboratory monitoring to detect medication toxicity, the risk of adverse events and patients'/caregivers' desire for safety should be balanced with the pain, inconvenience, and cost of phlebotomy and laboratory tests. The following recommendations pertain to specific medications or medication classes. If a child is receiving >1 medication, the more frequent schedule for laboratory testing is recommended. In formulating the recommendations below, the Voting Panel considered the US Food and Drug Administration (FDA) prescription drug labels (package inserts) in addition to the studies included in the systematic review.

For medications that are known teratogens (e.g., methotrexate, leflunomide), when applicable, pregnancy testing should be considered before usage, and counseling on effective methods of contraception is recommended (17). When required by the

Table 5. Medication monitoring*

	MTX†‡	SSZ†	LEF‡	Tocili-zumab	Ana-kinra	Tofacitinib	Canakinumab	NSAIDs†	HCQ	TNFi	Aba-tacept
CBC/diff. count and LFTs											
Baseline											
1–2 months after starting	X	X	X	X	X	X	X	–	–	–	–
Every 3–4 months thereafter§											
CBC/diff. count and LFTs											
Baseline	–	–	–	–	–	–	–	X	–	–	–
Every 6–12 months											
CBC/diff. count and LFTs											
Baseline	–	–	–	–	–	–	–	–	X	X	–
Once yearly											
Lipid panel											
Baseline	–	–	–	X	–	–	–	–	–	–	–
Every 6 months											
Lipid panel											
Baseline	–	–	–	–	–	X	–	–	–	–	–
4–8 weeks after starting											
Eye examination											
Baseline	–	–	–	–	–	–	–	–	X	–	–
Once yearly											
None required	–	–	–	–	–	–	–	–	–	–	X

* If the patient is receiving >1 medication, a more restrictive schedule should be used. MTX = methotrexate; SSZ = sulfasalazine; LEF = leflunomide; NSAIDs = nonsteroidal antiinflammatory drugs; HCQ = hydroxychloroquine; TNFi = tumor necrosis factor inhibitor; CBC/diff. = complete blood cell with differential; LFTs = liver function tests.
† Include renal function testing with laboratory studies.
‡ Pregnancy testing should be considered before use, and counseling on use of effective methods of contraception is recommended.
§ Should be rechecked sooner if dosage is increased.

FDA, a Risk Evaluation and Mitigation Strategy should be applied (18).

Baseline laboratory testing is conditionally recommended prior to treatment initiation, for all medications.

Baseline laboratory evaluation is recommended to identify potential contraindications to a specific treatment. This should include complete blood cell count (CBC) with differential cell count and liver function tests (LFTs) (e.g., alanine aminotransferase [ALT] and aspartate aminotransferase), plus renal function tests (e.g., blood urea nitrogen, creatinine, and urinalysis) for patients being treated with methotrexate, sulfasalazine, or nonsteroidal anti-inflammatory drugs (NSAIDs) and lipid profiles for patients being treated with tocilizumab and tofacitinib. Additional laboratory testing may be performed at the discretion of the treating clinician.

NSAIDs (all)

Monitoring via CBC counts, LFTs, and renal function tests every 6–12 months is conditionally recommended.

NSAIDs are known to be associated with gastrointestinal (GI) bleed risk and liver and kidney toxicity in adults with rheumatic diseases. Although these may be rare in children, the Voting Panel deemed it important to monitor for laboratory abnormalities periodically in children receiving long-term NSAIDs. Because GI distress when consistently taking NSAIDs is common, patients/caregivers strongly suggested that clinicians should inquire about and potentially treat GI symptoms, which may not always be spontaneously reported (19,20).

Methotrexate

Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is strongly recommended.

Voting panelists debated whether frequent methotrexate toxicity monitoring (as per the package instructions, i.e., CBC count monthly and renal/liver function every 1–2 months) should be recommended for children, given the low incidence of liver toxicity (21,22). However, rare potential for serious harm in children and consistency in monitoring schedule during pediatric-to-adult care transition influenced the panel's decision to provide a strong recommendation for frequent monitoring (23).

Decreasing the methotrexate dosage or withholding methotrexate is conditionally recommended if a clinically relevant elevation in LFT results or decreased neutrophil or platelet count is found.

The panel did not reach consensus on specific values to define elevated LFT results or reduced cell counts. Clinically

relevant laboratory abnormalities may include repetitive minor abnormalities or a single major abnormality. LFT results may be transiently elevated if testing is done within 2 days after administration of methotrexate; hence, testing within this window is discouraged.

Use of folic/folinic acid in conjunction with methotrexate is strongly recommended.

Use of folic/folinic acid with methotrexate may mitigate adverse events and improve tolerability (24,25).

Sulfasalazine

Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Recommended monitoring is less frequent than suggested in the package insert for sulfasalazine (which suggests CBC counts and LFTs every second week in the first 3 months, monthly during the next 3 months, and then every 3 months) because most children have fewer comorbidities and polypharmacy usage is rare, allowing for fewer drug interactions (26–28).

Decreasing the sulfasalazine dosage or withholding sulfasalazine is conditionally recommended if a clinically relevant elevation in LFT results or decreased neutrophil or platelet count is found.

While adverse reactions can be serious, including Stevens-Johnson syndrome or drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) (29), the Voting Panel thought the data were too limited to make this recommendation strong.

Leflunomide

Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Recommended LFT monitoring is less frequent than suggested in the leflunomide package insert (which recommends CBC counts and ALT testing monthly for 6 months and then every 6–8 weeks) (30) because most children have fewer comorbidities and polypharmacy usage is rare, allowing for fewer drug interactions (31).

Altering leflunomide administration is conditionally recommended if a clinically relevant elevation in LFT results occurs (temporary withholding of leflunomide if the ALT level is >3 times the upper limit of normal [ULN]), as per the package insert.

Elimination of leflunomide can be accelerated with the use of cholestyramine or activated charcoal (30), when required.

Hydroxychloroquine

Monitoring via CBC counts and LFTs annually is conditionally recommended.

As per the hydroxychloroquine package insert (32), periodic laboratory monitoring should be performed if patients are receiving prolonged therapy.

Baseline and annual retinal screening after starting hydroxychloroquine are conditionally recommended.

Yearly screening should be performed in pediatric patients, rather than waiting 5 years between baseline and subsequent annual screening as recommended for hydroxychloroquine-treated adults (33). The cumulative and developmental effects of hydroxychloroquine are a concern because children may be receiving treatment for prolonged periods and may not be able to articulate vision concerns. Baseline retinal screening should be completed as soon as possible and combined with screening for uveitis when feasible. Treatment does not need to be delayed for initial retinal screening.

Tumor necrosis factor inhibitors (TNFi) (all)

Monitoring via CBC counts and LFTs annually is conditionally recommended.

As per package inserts, cytopenias and abnormal LFTs have been reported in association with TNFi treatment. Therefore, evaluation yearly at minimum is recommended (34,35).

Abatacept

Doing no routine laboratory monitoring is conditionally recommended.

In placebo-controlled clinical trials of abatacept for JIA, children had similar CBC counts and LFT results irrespective of treatment arm (36), and no laboratory monitoring is suggested in the package insert (37). The decision to perform laboratory monitoring may be discussed with patients/caregivers who, like some of the voting panelists, may prefer routine monitoring to identify potential adverse events, even if rare.

Tocilizumab

Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Monitoring of lipid levels every 6 months is conditionally recommended, as per the package insert.

Altering tocilizumab administration is conditionally recommended if monitoring reveals elevated LFT results (if 1–3 times the ULN, decrease the dosage or increase the interval between doses, if >3 times the ULN, withhold administration, if >5 times the ULN, discontinue treatment), neutropenia (500–1,000/mm^3), or thrombocytopenia (50,000–100,000/mm^3), as per the package insert.

As per the package insert, initiation of tocilizumab treatment is not recommended in patients with elevated LFT results (>1.5 times the ULN) (38). In patients in whom LFT results become highly elevated (>5 times the ULN), treatment should be discontinued. The package insert does state that the decision to discontinue tocilizumab due to a laboratory abnormality should be based on the medical assessment of the individual patient. For that reason, this recommendation is conditional.

Anakinra

Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Abnormal LFTs and neutropenia may occur with the use of anakinra (39). For that reason, as well as the severity of the underlying disease, regular monitoring should be performed.

Canakinumab

Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Abnormal LFT results and cytopenias were noted during a phase III clinical trial of canakinumab for systemic JIA (40). For that reason, as well as the severity of the underlying disease, regular monitoring should be performed.

Tofacitinib

Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Monitoring of lipid levels 1–2 months after starting treatment is conditionally recommended, as per the package insert.

Altering tofacitinib administration is strongly recommended if monitoring reveals laboratory abnormalities of concern. Specifically, medication should be discontinued if the hemoglobin level is <8 gm/dl or decreases by >2 gm/dl, or for severe neutropenia (<500/mm^3) or lymphopenia (<500/mm^3), as per the package insert.

Data on tofacitinib were not part of the initial literature review, but the panel considered it important to include this recommendation because in 2020 tofacitinib was approved by the FDA for treatment of JIA (41). An additional Voting Panel session was organized for this purpose.

Infection surveillance (Table 6)

Tuberculosis (TB)

TB screening is conditionally recommended prior to starting biologic disease-modifying antirheumatic drug (DMARD) therapy and when there is a concern for TB exposure thereafter.

Concern for TB exposure should be interpreted broadly and could include contact with someone with active TB, travel to locations where TB is endemic, contact with high-risk individuals (e.g., prisoners, visitors from TB-endemic areas), or living in communities with a higher frequency of TB (42,43). The conditional recommendation reflects 2 major concerns: In certain urgent clinical situations, the harms of waiting for results of TB screening may outweigh the benefits of treatment. For example, in a child with active systemic JIA and macrophage activation syndrome (MAS), treatment should not be delayed pending TB screening results. Annual screening for TB can pose problems for children and families. Insurers or institutions may require a specific method that is potentially problematic (44,45). For example, TB screening may be done by questionnaire; however, this depends on knowledge of exposure. The interferon-γ release assay is expensive, not valid in young children, and subject to frequent indeterminate results, particularly during anergy. Tuberculin skin testing is user dependent and inconvenient because 2 visits are required. In addition, false-positive results often lead to unnecessary chest radiography and isoniazid treatment. For children living in areas with a low prevalence of TB, mandatory annual laboratory-based TB screening represents a high burden of cost, inconvenience, and pain that is not supported by the literature reviewed.

Viral infections

Voting panelists could not reach consensus on whether all children with JIA should have antibody titers for specific infections (e.g., measles, varicella, hepatitis B, hepatitis C) checked prior to starting immunosuppressive medication, although more panelists were against this practice than for it. Some panelists believed the information might be useful for risk management in case of an outbreak or exposure. Most believed that screening a fully immunized child was of low benefit and might delay treatment and incur unnecessary cost. Although

Table 6. Infection surveillance/immunizations*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
No consensus achieved.	Very low	PICO 45. Should all children with JIA have infection titers (measles, varicella, hepatitis B, hepatitis C) checked prior to starting immunosuppressive medication?	164–166
Immunization is **conditionally** recommended for children with active non-systemic JIA who have not yet been immunized for measles, mumps, rubella, and/or varicella prior to starting immunosuppressive medications.	Very low	PICO 46. Should children with JIA with no evidence of immunity to important infections have a booster immunization prior to starting immunosuppressive medication?	166
TB screening is **conditionally** recommended prior to starting biologic DMARD therapy and when there is a concern for TB exposure thereafter.	Very low	PICO 47. Should screening for TB be done prior to starting biologic DMARD therapy and then annually in children with JIA?	167–169
	Very low	PICO 48. In children with JIA receiving biologic DMARD therapy, is there a preferred method of TB screening?	169–171
Immunizations (live and inactivated) are **strongly** recommended for children with JIA who are not receiving immunosuppressive treatment.	Very low	PICO 49. In children with JIA not receiving immunosuppressive treatment, do inactivated or live attenuated vaccines result in flare of disease?	172–175
Annual inactivated influenza immunization is **strongly** recommended for all children with JIA.	Low	PICO 50. In children with JIA not receiving immunosuppressive treatment, are patients able to develop protective antibodies against infections targeted by the vaccine?	175–179
		PICO 52. In children with JIA receiving immunosuppressive treatment, are patients able to develop protective antibodies against infections targeted by the vaccine?	184–195
Inactivated vaccines are **strongly** recommended for children who are receiving immunosuppressive treatment.	Very low	PICO 51. In children with JIA receiving immunosuppressive treatment, do inactivated vaccines result in flare of disease?	180–184
Live attenuated vaccines are **conditionally** recommended *against* in children with JIA who are receiving immunosuppressive treatment.	Low	PICO 53. In children with JIA receiving immunosuppressive treatment, can treatment with live attenuated vaccines be given safely (initial dose, booster dose)?	195–198
Vaccines are **strongly** recommended for household contacts of children with JIA who are receiving immunosuppressive treatment.	Very low	PICO 54. Can live attenuated vaccines be used safely in the households of children with JIA receiving immunosuppressive treatment?	198

* PICO = Patient/Population, Intervention, Comparison, and Outcomes; JIA = juvenile idiopathic arthritis; TB = tuberculosis; DMARD = disease-modifying antirheumatic drug.
† In Supplementary Appendix 3, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42036/abstract.

screening for hepatitis B and C is done in adults prior to treatment with DMARDs, most children are effectively immunized against hepatitis B as infants (46), and the number of children below the age of 19 years with hepatitis C in the US remains exceedingly low (47).

Immunizations (Table 6)

Because some patients/caregivers have concerns about the safety of vaccines in JIA, clinicians must discuss with families the evidence that strongly supports their benefits and safety. Whenever possible, immunizations should be administered according to the schedule recommended by the ACIP and the AAP or corresponding national recommendations. As immunization schedules are frequently updated, clinicians should ensure that they are using the most recent versions (48). Multiple cohort studies have demonstrated that most children with JIA mount a protective response after immunizations and that immunizations do not cause disease flare (49–52).

Annual inactivated influenza immunization is strongly recommended for all children with JIA

All children with JIA, including children receiving immunosuppressive medication, should receive inactivated influenza immunizations annually (53). This recommendation is strong despite very low evidence in JIA, given the overwhelming preponderance of supporting literature in other inflammatory diseases and the risk of severe infection (54–57). Intranasal influenza immunization is contraindicated for children with JIA who are receiving immunosuppressive treatment, as it is a live attenuated immunization.

Table 7. Imaging*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
Use of radiography as a screening test prior to advanced imaging, for the purpose of identifying active synovitis or enthesitis, is **strongly** recommended *against*.	Very low	PICO 55. In children with JIA, is any specific imaging technique recommended to best detect inflammation and damage, make a diagnosis, and predict structural damage, flare, or treatment response?	199–268
Imaging guidance is **conditionally** recommended for use with intraarticular glucocorticoid injections of joints that are difficult to access, or to specifically localize the distribution of inflammation.	Very low	PICO 56. In children with JIA who require intraarticular glucocorticoid injections, should injections be done with imaging guidance?	269–279

* PICO = Patient/Population, Intervention, Comparison, and Outcomes; JIA = juvenile idiopathic arthritis.
† In Supplementary Appendix 3, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42036/abstract.

Immunizations (live attenuated and inactivated) are strongly recommended for children with JIA who are not receiving immunosuppressive treatment

Children with JIA have a higher risk of severe infection compared to unaffected children, making adequate protections against infection essential (58). Considerations of the relative degree of immunosuppression from various immunosuppressive medications used for JIA is beyond the scope of this project. To err on the side of safety, these recommendations apply equally to any child receiving an immunosuppressive medication for JIA (e.g., DMARDs, long-term systemic glucocorticoids) (59).

Inactivated vaccines are strongly recommended for children with JIA who are receiving immunosuppressive treatment.

Persons with JIA should receive inactivated vaccines as per location-specific, published age-related schedule. Specifically, children undergoing immunosuppressive treatment should receive the 23-valent pneumococcal polysaccharide vaccine in addition to the 13-valent pneumococcal conjugate vaccine recommended for all children (60,61).

Live attenuated vaccines are conditionally recommended *against* in children with JIA who are receiving immunosuppressive treatment.

As reported by the US Centers for Disease Control and Prevention (CDC), severe complications have followed vaccination with certain live attenuated viral and bacterial vaccines among immunosuppressed persons (62). Therefore, guidelines recommend that persons with most forms of altered immunocompetence should not receive live attenuated vaccines. According to the CDC, live-virus vaccination should be deferred for 1–6 months after discontinuation of immunosuppressive treatment, depending on the specific agent (62). There is some evidence that booster immunization with live attenuated vaccines may be safe for children with JIA who are receiving certain specific immunosuppressants (52,63). More work is needed to support a formal recommendation in this setting, as studies thus far have been underpowered to detect rare, serious harms.

Immunization is conditionally recommended for children with active non-systemic JIA who have not yet been immunized for measles, mumps, rubella, and/or varicella prior to starting immunosuppressive medications.

This recommendation excludes active, untreated systemic JIA in which delaying treatment initiation for vaccinations may be prohibitive. As per the CDC, immunosuppressive therapy should not be initiated until 4 weeks after administration of a live vaccine and ideally 2 weeks after administration of an inactivated vaccine. If withholding/delaying medication is not feasible, live-attenuated vaccine immunization should be deferred and given at a later time when disease is in remission and the child is no longer being treated (64).

Vaccines are strongly recommended for household contacts of children with JIA who are receiving immunosuppressive treatment.

Immunization of household members of immunosuppressed children is critical to diminish exposure in the home. Household contacts and other close contacts of persons with altered immunocompetence should receive all age- and exposure-appropriate vaccines, whether inactivated or live, with the exception of smallpox vaccine (59,65). If a family member has received varicella vaccine and develops a rash, direct contact should be avoided until the rash resolves. Likewise, all members of the household should wash their hands after changing the diaper of an infant who recently received rotavirus vaccine, to minimize transmission. If concerns remain, CDC or local guidelines can be reviewed prior to immunization.

Imaging (Table 7)

Use of radiography as a screening test prior to advanced imaging, for the purpose of identifying active synovitis or enthesitis, is strongly recommended *against*.

Radiography is not sensitive enough to assess joint inflammation and enthesitis in children and may delay clinically appropriate imaging and treatment (66–68). Unnecessary radiation can result in significant harm to developing children (69). Conventional

radiography should be restricted to the assessment of JIA-associated damage or to investigate alternative diagnoses.

Imaging guidance is conditionally recommended for use with intraarticular glucocorticoid injections of joints that are difficult to access, or to specifically localize the distribution of inflammation.

This recommendation includes ultrasound and/or fluoroscopy. Specific joints that may be difficult to access include sacroiliac joints, hips, TMJs, shoulder, midfoot, and subtalar joints. This recommendation is conditional because it is dependent on the skill of the practitioner, availability of imaging, costs, and risk of delay in treatment (70–72).

DISCUSSION

The recommendations presented in this guideline are a companion to those published in 2019 (3,4) and concurrently (73) and cover areas not previously addressed in JIA: nonpharmacologic treatments, medication monitoring, immunization, and imaging. Similar to recommendations made for oligoarthritis, TMJ arthritis, and systemic JIA with and without MAS, one must view this guideline as a road map for future study (Supplementary Appendix 7, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42036/abstract). Most of the available evidence was very low quality for the relevant PICO questions, contributing to 23 of the 33 recommendations being conditional. None of the recommendations were supported by moderate- or high-quality evidence.

Nowhere is the discrepancy between patient/caregiver interest and available data more evident than in the consideration of nonpharmacologic therapies, for which recommendations were included at patient/parent request. Use of specific diets and supplements was discussed extensively by the patient/caregiver panel, including sharing of suggested regimens and reference materials. There was a general belief that disease manifestations could be ameliorated by changes in foods consumed and great interest in participating in formal research studies on nutritional interventions. Most panelists recognized the importance of PT/OT, and inclusion of PT and OT specialists on the Voting Panel would allow for more specific recommendations in future guidelines.

Likewise, patients and caregivers discussed the stress of dealing with chronic illness and the need for mental health interventions. As recently as 2017, when the scope of this project was established, mental health care for children and families affected by rheumatic diseases was not a major focus. For this reason, although mental health was recognized by the Voting Panel as important, it was not formally addressed in this guideline. Future guidelines should include recommendations addressing mental health screening and treatments, with input from mental health professionals on the Voting Panel. This is particularly important given the impact of the COVID-19 pandemic on the mental health of persons with chronic disease (74).

Medication monitoring remains especially challenging in JIA, and balancing safety, cost, pain, and inconvenience can be very difficult. Some panel members asserted that monitoring was perhaps less important in a generally healthy pediatric population relative to adults with comorbidities. Due to the low frequency of serious comorbidities and interacting medications, and limited-to-no exposure to alcohol and other toxins, laboratory abnormalities requiring medication discontinuation are rare in children with JIA. However, other panel members believed strongly that monitoring needs to be routinely performed to identify rare but serious adverse events. Recommendations as written attempted to balance these concerns. Future research and guidelines should consider altered, less frequent monitoring schedules for younger children, given the potentially lower risks of toxicity and greater risks of frequent testing at the youngest ages.

The list of available immunosuppressive medications for JIA for which monitoring is required has grown substantially and will continue to expand. Two new agents were recently approved for use in polyarticular-course JIA: golimumab (a TNFi) and tofacitinib (a JAK inhibitor) (41,75). With regard to laboratory testing to detect abnormalities in monitoring for toxicity, voting panelists could not agree on a single definition of "clinically relevant" abnormal results and left this to the discretion of treating clinicians. Caregivers and patients expressed the challenges of balancing the need to ensure medication safety with the cost and inconvenience associated with blood withdrawal. It is hoped that in the future, effective, reliable treatments that require less monitoring will be available for JIA.

Voting panelists did believe strongly that age must be taken into consideration in requirements for infection screening in the US prior to initiation of treatment with DMARDs. TB, hepatitis B, and hepatitis C are extremely rare in fully immunized nonimmigrant children in the US, and annual TB screening presents a large and unnecessary burden. There were engaged discussions about screening for viral infections prior to the use of DMARDs; however, most thought that lack of immunity in a child known to be immunized was likely to be rare. Even if antibody titers were low or absent after vaccination, cell-mediated immunity was considered likely to be present.

In light of the COVID-19 pandemic, discussion of immunizations in these guidelines proved to be extremely timely. Despite the potential severity of vaccine-preventable infections in immunosuppressed populations, vaccine hesitancy remains common. Nonetheless, preventing infectious illnesses in an immunosuppressed patient population is critical. Many families have concerns regarding vaccine safety, immunogenicity, risk of flare, and other potential long-term consequences. Studies in JIA have consistently demonstrated the safety and effectiveness of vaccines to induce protective immune responses. Regarding immunization for COVID-19, available immunizations vary by

age, accessibility, and country. There are currently no preferences for a specific vaccine in a given population of children with rheumatic disease. Physicians should refer to local recommendations. At the time this manuscript was approved for publication, the Pfizer-BioNTech COVID-19 vaccine was approved in the US for adolescents age ≥16 years (76) and authorized for emergency use in children 5–15 years of age (77,78). No vaccines for COVID-19 were yet available for younger children, although studies are ongoing. As none of the currently available vaccines against COVID-19 are live vaccines, recommendations should be similar to those stated above for inactivated vaccines. While specific guidance on immunizing children with rheumatic diseases against COVID-19 is still lacking, the ACR has published guidance on COVID-19 vaccines for adults with rheumatic and musculoskeletal diseases (79). Patients and family members have articulated the importance of health care providers for reliable medical information. We must be mindful that clinicians are trusted sources of information about this important public health issue and should discuss immunizations with their patients.

With regard to imaging, it is clear that different modalities are appropriate for different indications. Radiographs are not useful for evaluation of soft tissue disease, and continued third-party payor requirements for radiographs prior to any and all magnetic resonance imaging (MRI) are a waste of resources and a potential hazard to persons with JIA. MRI itself may require sedation, and there is concern that repeated sedation in young children may carry risks (80). More research is needed to define and standardize the best approaches to imaging in children with JIA for different diagnostic and disease management decision-making purposes.

Addressing each area of the JIA guidelines at the same time proved to be a Herculean task. This update of the ACR JIA guidelines has taken 4 years to complete, leading to 4 manuscripts; certain areas are already ready for further updates. Health care around the world is quickly changing in unforeseen ways, and rheumatologists have been thrust into the forefront of recent pandemic developments in an unparalleled manner (81). The pace of change will likely only increase, and guidelines will need to be updated nimbly and more frequently over time.

The low quality of evidence supporting most of the recommendations underscores the importance of clinical judgment and shared decision-making in everyday care of patients with JIA. Similarly, these guidelines and the many uncertainties therein represent a powerful reminder of the need for more high-quality evidence to support (or refute) current practices and to improve disease management in—and well-being of—all individuals living with JIA.

In conclusion, this 2021 updated ACR guideline for JIA recommends the use of PT and OT interventions; a healthy, well-balanced, age-appropriate diet; specific laboratory monitoring for different antirheumatic medications; widespread use of immunizations; and need for shared decision-making with patients/caregivers. The JIA guidelines will continue to be updated as new evidence emerges.

ACKNOWLEDGMENTS

We thank Jennifer Horonjeff who (along with author Katherine Murphy) participated in the Patient Panel meeting. We thank the ACR staff, including Regina Parker for assistance in coordinating the administrative aspects of the project and Cindy Force for assistance with manuscript preparation. We thank Janet Waters for assistance in developing the literature search strategy as well as performing the initial literature search and update searches.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Onel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Onel, Horton, Lovell, Shenoi, Cuello, Lee, Murphy, Barbar-Smiley, Edelheit, Sullivan, Turner.

Acquisition of data. Onel, Horton, Lovell, Shenoi, Kimura, Lee, Murphy, Nigrovic, Ombrello, Rabinovich, Twilt, Barbar-Smiley, Cooper, Edelheit, Gillispie-Taylor, Hays, Mannion, Peterson, Flanagan, Saad, Sullivan, Szymanski, Trachtman, Reston.

Analysis and interpretation of data. Onel, Horton, Lovell, Shenoi, Cuello, Angeles-Han, Becker, Cron, Feldman, Ferguson, Gewanter, Guzman, Kimura, Nigrovic, Ombrello, Rabinovich, Tesher, Twilt, Klein-Gitelman, Cooper, Edelheit, Gillispie-Taylor, Mannion, Sullivan, Szymanski, Trachtman, Turgunbaev, Veiga, Reston.

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Arthritis & Rheumatology
Vol. 74, No. 4, April 2022, pp 553–569
DOI 10.1002/art.42037
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2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis

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Objective. To provide updated guidelines for pharmacologic management of juvenile idiopathic arthritis (JIA), focusing on treatment of oligoarthritis, temporomandibular joint (TMJ) arthritis, and systemic JIA with and without macrophage activation syndrome. Recommendations regarding tapering and discontinuing treatment in inactive systemic JIA are also provided.

Methods. We developed clinically relevant Patient/Population, Intervention, Comparison, and Outcomes questions. After conducting a systematic literature review, the Grading of Recommendations Assessment, Development and Evaluation approach was used to rate the quality of evidence (high, moderate, low, or very low). A Voting Panel including clinicians and patients/caregivers achieved consensus on the direction (for or against) and strength (strong or conditional) of recommendations.

Results. Similar to those published in 2019, these JIA recommendations are based on clinical phenotypes of JIA, rather than a specific classification schema. This guideline provides recommendations for initial and subsequent treatment of JIA with oligoarthritis, TMJ arthritis, and systemic JIA as well as for tapering and discontinuing treatment in subjects with inactive systemic JIA. Other aspects of disease management, including factors that influence treatment choice and medication tapering, are discussed. Evidence for all recommendations was graded as low or very low in quality. For that reason, more than half of the recommendations are conditional.

Conclusion. This clinical practice guideline complements the 2019 American College of Rheumatology JIA and uveitis guidelines, which addressed polyarthritis, sacroiliitis, enthesitis, and uveitis. It serves as a tool to support clinicians, patients, and caregivers in decision-making. The recommendations take into consideration the severity of both articular and nonarticular manifestations as well as patient quality of life. Although evidence is generally low quality and many recommendations are conditional, the inclusion of caregivers and patients in the decision-making process strengthens the relevance and applicability of the guideline. It is important to remember that these are recommendations. Clinical decisions, as always, should be made by the treating clinician and patient/caregiver.

INTRODUCTION

Reflecting the changing medical landscape, the American College of Rheumatology (ACR) regularly updates clinical practice guidelines and plans to review these annually and update as needed. The process for updating the 2011 and 2013 juvenile idiopathic arthritis (JIA) guidelines (1,2) began in 2017. Important clinical topics for consideration were first identified at a meeting to define the scope of the guidelines. Advances in the treatment of JIA and better understanding of pathogenesis dictated separating this clinical practice guideline into several parts due to the breadth of topics. The first part, addressing polyarthritis, sacroiliitis, enthesitis, and uveitis, was published in 2 articles in 2019 (3,4). The second part, presented here in 2 articles, covers 1) oligoarthritis, temporomandibular joint (TMJ) arthritis, and systemic JIA, and 2) nonpharmacologic treatments, patient monitoring, immunizations, and imaging (5). The methods and literature review described below reflect the unified process used for the second part of these guidelines, including both articles. Recommendations were intended to be complementary to the 2019 guidelines and are grouped based on disease phenotype and severity, not by specific classification criteria, reflecting decision-making in clinical practice.

Following the selection of topics, we developed clinically relevant Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions. Using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, recommendations were then developed based on the best available evidence for commonly encountered clinical scenarios. Prior to final voting, input was sought from relevant stakeholders, including a panel of young adults with JIA and caregivers of children with JIA, to consider their values and perspectives in making recommendations. Both the patient/caregiver and guideline Voting Panels stressed the need for individualized treatment while being mindful of available evidence.

METHODS

This guideline followed the ACR guideline development process and ACR policy guiding management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), which include GRADE methodology (6,7) and adheres to Appraisal of Guidelines, Research and Evaluation criteria (8). Supplementary Appendix 1 (available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42037/abstract)

This article is published simultaneously in *Arthritis Care & Research*.

Supported by the American College of Rheumatology. Dr. Horton's work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant K23-AR-070286). Dr. Ombrello's work was supported by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant AR-041198).

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.42037&file=art42037-sup-0001-Disclosureform.pdf.

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Submitted for publication July 7, 2021; accepted in revised form November 23, 2021.

includes a detailed description of the methods. Briefly, the Core Leadership Team (KBO, DBH, DJL, SS) drafted clinical PICO questions. PICO questions were revised and finalized based on feedback from the entire guideline development group and the public. The Literature Review Team performed systematic literature reviews for each PICO (for search terms, see Supplementary Appendix 2, https://onlinelibrary.wiley.com/doi/10.1002/art.42037/abstract), graded the quality of evidence (high, moderate, low, or very low), and produced the evidence report (Supplementary Appendix 3, https://onlinelibrary.wiley.com/doi/10.1002/art.42037/abstract). It should be noted that GRADE methodology does not distinguish between lack of evidence (i.e., none) and very low–quality evidence. The Core Team defined multiple critical study outcome(s) for PICOs relevant to each JIA phenotype (Supplementary Appendix 4, https://onlinelibrary.wiley.com/doi/10.1002/art.42037/abstract).

A panel of 15 members, including young adults with JIA and caregivers of children with JIA, met virtually (moderated by the principal investigator [KBO]), reviewed the evidence report, and provided input to the Voting Panel. Two members of this panel were also members of the Voting Panel to ensure that the patient voice was part of the entire process. The Voting Panel reviewed the evidence report and patient/caregiver perspectives and then discussed and voted on recommendation statements. Consensus required ≥70% agreement on both direction (for or against) and strength (strong or conditional) of each recommendation, as per ACR practice. A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when the decision is sensitive to individual patient preferences, or when costs are expected to impact the decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision-making. Examples of each class of pharmacologic intervention addressed in the recommendations are shown in Table 1.

Rosters of the Core Leadership Team, Literature Review Team, and both panels are included in Supplementary Appendix 5 (https://onlinelibrary.wiley.com/doi/10.1002/art.42037/abstract).

Guiding principles

The development of the recommendations presented herein was guided by the following principles:

1. Consistent with the ACR's 2019 JIA guidelines, these recommendations are for persons already diagnosed as having JIA.
2. Aside from poor prognostic features specified within the recommendations themselves (e.g., specific joints for oligoarthritis, macrophage activation syndrome [MAS]), coexisting extraarticular conditions that would influence disease management, such as uveitis, psoriasis, or inflammatory bowel disease, are not addressed within these guidelines.
3. Recommendations are intended to be used by all clinicians caring for persons with JIA and assume that patients do not have contraindications to the recommended pharmacologic treatments.
4. Longer-term glucocorticoid therapy in childhood is not appropriate because of its effects on bone health and growth. Thus, wherever glucocorticoids are suggested, recommended treatment should be limited to the lowest effective dose for the shortest duration possible.
5. Shared decision-making with families and patients is important when considering treatment options.

RESULTS/RECOMMENDATIONS

The initial literature review included topics addressed in this report and in the second report (9), and identified 4,308 articles in searches for all PICO questions through August 7, 2019. A July 9, 2020 search update identified 367 more references, for a total of 4,675 articles after duplicates and non-English publications were removed. After exclusion of 2,291 titles and abstracts, 2,384 full-text articles were screened. Of these, 1,939 were excluded (Supplementary Appendix 6, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/

Table 1. Classes of interventions

Nonsteroidal antiinflammatory drugs	Any at therapeutic dosing (ibuprofen, naproxen, tolmetin, indomethacin, meloxicam, nabumetone, diclofenac, piroxicam, etodolac, celecoxib)
Conventional synthetic disease-modifying antirheumatic drugs	Methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, calcineurin inhibitors (cyclosporin A, tacrolimus)
Biologic disease-modifying antirheumatic drugs	Tumor necrosis factor inhibitors (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol); other biologic response modifiers (abatacept, tocilizumab, anakinra, canakinumab)
Glucocorticoids	Oral (any); intravenous (any); intraarticular (triamcinolone acetonide, triamcinolone hexacetonide)

Table 2. Strength of recommendations and quality of supporting evidence*

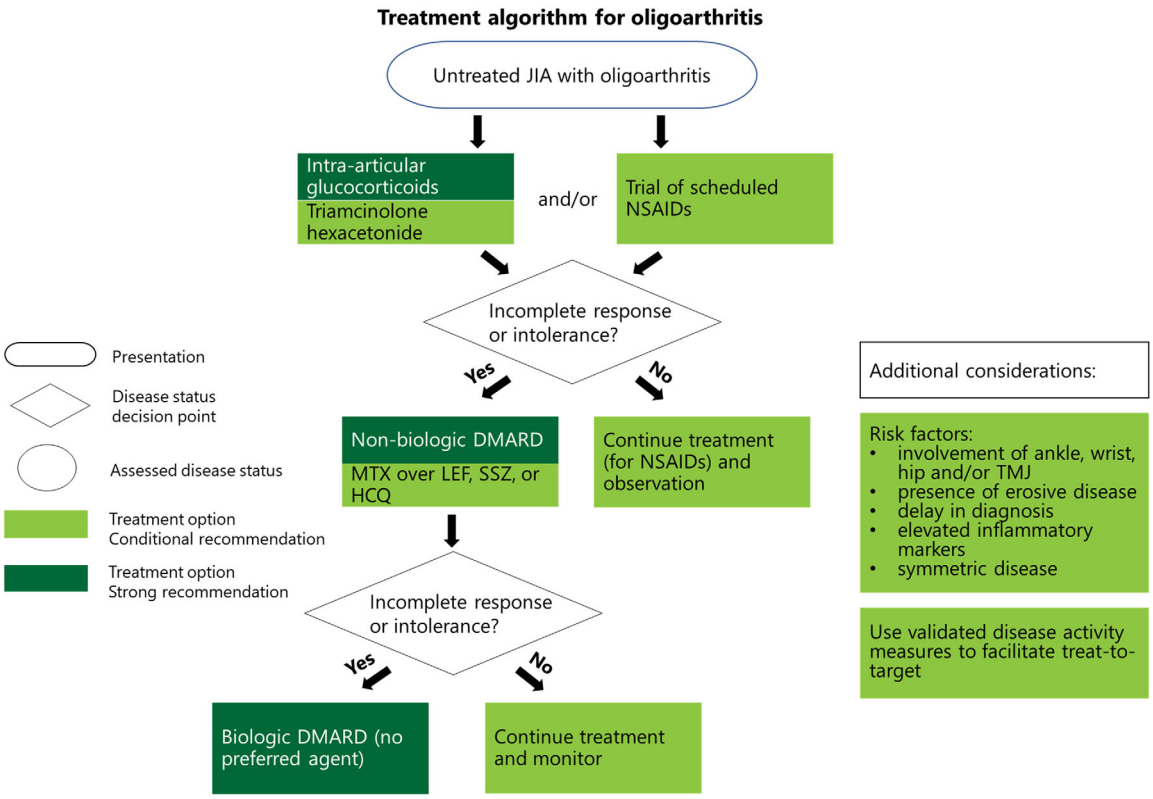
	Strength of recommendation			Quality of supporting evidence			
	No. of recommendations	Conditional	Strong	Very low	Low	Moderate	High
Oligoarthritis	9	5	4	7	2	0	0
TMJ arthritis	7	6	1	7	0	0	0
Systemic JIA	9	5	4	9	0	0	0
Total	25	16	9	23	2	0	0

* TMJ = temporomandibular joint; JIA = juvenile idiopathic arthritis.

art.42037/abstract), leaving 445 articles to be considered for the evidence report. Ultimately, 336 articles were matched to PICO questions and included in the final evidence report. Quality of evidence was uniformly low or very low; 17 PICO questions lacked any associated evidence and as per GRADE methodology were categorized as very low (Tables 2–7). The recommendations that follow are based on 62 PICO questions. Several PICO questions were split into 24 sub-PICO questions to improve specificity. Nine questions initially posed were discarded by the Voting Panel because of redundancy or lack of relevance. Final recommendations are described below and in Tables 3–7, which include reference(s) to which PICO question(s) in the evidence report correspond to the recommendation statement.

Active oligoarthritis (Figure 1 and Table 3)

Oligoarthritis refers to JIA presenting with involvement of ≤4 joints without systemic manifestations. It may include patients with different categories of JIA (10) but who share in common limited numbers of joints involved; guidance for patients with active uveitis, sacroiliitis, or enthesitis can be found in the 2019 guidelines (3,4). TMJ arthritis is discussed separately.



DMARD = disease-modifying antirheumatic drug, HCQ = hydroxychloroquine, JIA = juvenile idiopathic arthritis, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal antiinflammatory drugs, SSZ = sulfasalazine, TMJ = temporomandibular joint

Figure 1. Treatment algorithm for oligoarthritis.

Table 3. Oligoarticular JIA*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
A trial of scheduled NSAIDs is **conditionally** recommended as part of initial therapy.	Very low	PICO 1. In children with oligoarticular JIA, should a trial of scheduled NSAIDs be recommended?	6–9
IAGCs are **strongly** recommended as part of initial therapy.	Very low	PICO 2. In children with oligoarticular JIA, should adding IAGCs to initial therapy be recommended?	10–19
Triamcinolone hexacetonide is **strongly** recommended as the preferred agent.	Low	PICO 4. In children with oligoarticular JIA, should a specific steroid type be recommended for intraarticular injection?	21–27
Oral glucocorticoids are **conditionally** recommended *against* as part of initial therapy.	Very low	PICO 3. In children with oligoarticular JIA, should adding oral steroids to initial therapy be recommended?	19–20
Conventional synthetic DMARDs are **strongly** recommended if there is inadequate response to scheduled NSAIDs and/or IAGCs. MTX is **conditionally** recommended as a preferred agent over LEF, SSZ, and HCQ (in that order).	Low (MTX); Very low (LEF, SSZ, HCQ)	PICO 5. In children with oligoarticular JIA, should DMARD therapies be recommended, and should there be any preferred order of treatment: MTX (subcutaneous or oral), LEF, SSZ, and/or HCQ?	28–41
Biologic DMARDs are **strongly** recommended if there is inadequate response to or intolerance of NSAIDs and/or IAGCs and at least 1 conventional synthetic DMARD. There is no preferred biologic DMARD.	Very low	PICO 6. In children with oligoarticular JIA, should biologic therapies be recommended, and should there be any preferred order of treatment: TNFi treatment, biologic treatments with other mechanisms of action?	42–47
Consideration of risk factors for poor outcome (e.g., involvement of ankle, wrist, hip, sacroiliac joint, and/or TMJ, presence of erosive disease or enthesitis, delay in diagnosis, elevated levels of inflammation markers, symmetric disease) is **conditionally** recommended to guide treatment decisions.	Very low	PICO 9. In children with oligoarticular JIA, should poor prognostic features alter the treatment paradigm? PICO 19. In children with JIA with active TMJ arthritis, should poor prognostic features alter the treatment paradigm?	51–52 60
Use of validated disease activity measures is **conditionally** recommended to guide treatment decisions, especially to facilitate treat-to-target approaches.	Very low	PICO 10. In children with oligoarticular JIA, should disease activity measures alter the treatment paradigm?	52

* JIA = juvenile idiopathic arthritis; PICO = Patient/Population, Intervention, Comparison, and Outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; IAGCs = intraarticular glucocorticoids; DMARDs = disease-modifying antirheumatic drugs; MTX = methotrexate; LEF = leflunomide; SSZ = sulfasalazine; HCQ = hydroxychloroquine; TNFi = tumor necrosis factor inhibitor; TMJ = temporomandibular joint.
† In Supplementary Appendix 3, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42037/abstract.

Nonsteroidal antiinflammatory drugs (NSAIDs)

A trial of scheduled NSAIDs is conditionally recommended as part of initial therapy for active oligoarthritis.

NSAIDs have long been the cornerstone of treatment for oligoarthritis and can ease discomfort (11–13). However, the initial NSAID trial should be brief due to potential adverse effects (e.g., gastritis, bruising) and limited efficacy (unless inactive disease is achieved). Voting panelists could not agree on the appropriate duration of initial use before escalating therapy, as some panelists prefer that the use of NSAIDs be avoided altogether.

Glucocorticoids

Intraarticular glucocorticoids (IAGCs) are strongly recommended as part of initial therapy for active oligoarthritis.

Triamcinolone hexacetonide is strongly recommended as the preferred agent.

Although the evidence is of low quality, IAGCs are strongly recommended due to low potential of adverse effects and high likelihood of sustained response (14–16). Patients and caregivers agreed with regard to the utility of IAGC but voiced

concerns over the need for sedation in younger children and associated risks.

Despite an overall grading of the evidence as low, the panel was convinced by published randomized trials and large observational studies (17–19) that triamcinolone hexacetonide results in more durable clinical responses than triamcinolone acetonide, leading to the strong recommendation. Triamcinolone hexacetonide has been unavailable in the US for several years. However, very recently, the US Food and Drug Administration (FDA) has allowed the importation of one particular formulation of triamcinolone hexacetonide specifically for joint injections in patients with JIA to address this identified unmet medical need.

Oral glucocorticoids are conditionally recommended *against* as part of initial therapy for active oligoarthritis.

If, despite recommendations against, oral glucocorticoids are given to quickly alleviate severe symptoms when an IAGC is not available or feasible, or prior to the onset of action of disease-modifying antirheumatic drugs (DMARDs), treatment should be limited to the lowest effective dose for the shortest duration possible (20,21).

Conventional synthetic DMARDs (csDMARDs)

Conventional synthetic DMARDs are strongly recommended if there is an inadequate response to scheduled NSAIDs and/or IAGCs for active oligoarthritis.

Methotrexate is conditionally recommended as a preferred agent over leflunomide, sulfasalazine, or hydroxychloroquine (in that order).

Despite an absence of comparator trials, methotrexate is the preferred agent, given the preponderance of evidence showing its long-term safety and efficacy in children (22–24). Because the tolerability of methotrexate is variable, additional treatment options are provided (25–28).

With regard to the route of administration of methotrexate, the 2019 JIA guidelines conditionally recommended subcutaneous over oral administration for polyarthritis (3). This recommendation was conditional because the supporting evidence was of very low quality and patient preferences may guide choice of route of administration. There is little reason to suggest that methotrexate should be used differently in oligoarthritis than in polyarthritis.

Biologic DMARDs (bDMARDs)

Biologic DMARDs are strongly recommended if there is inadequate response to or intolerance of NSAIDs and/or IAGCs and at least 1 csDMARD for active oligoarthritis.

There is no preferred bDMARD.

Biologic DMARDs are preferred over combining csDMARDs or switching to a different csDMARD, due to a greater likelihood that bDMARDs will yield rapid and sustained improvement in JIA (29,30). While combination csDMARDs have been used for the treatment of rheumatoid arthritis in adults, in children the combination appears to be less effective and less tolerable (31). For these reasons, this recommendation is strong.

Although tumor necrosis factor inhibitors (TNFi) are the most commonly used bDMARDs in children (32–34), other bDMARDs of proven efficacy in the treatment of JIA may be used. In the absence of head-to-head trials in children with oligoarthritis (35), bDMARD selection may be driven by specific provider and patient/caregiver preferences and circumstances, with the exception of interleukin-1 (IL-1) inhibitors, which are preferentially used for the treatment of systemic JIA (29,36–38).

Risk factors for poor prognosis and disease activity measures

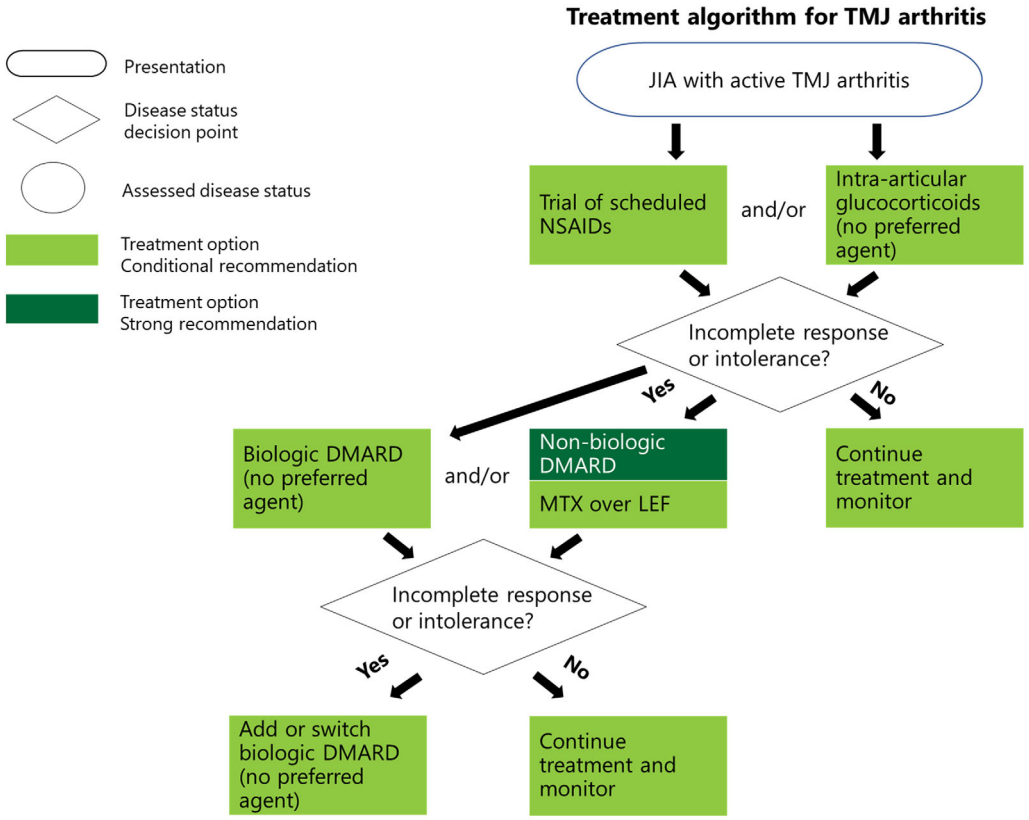
Consideration of risk factors for poor outcome (e.g., involvement of ankle, wrist, hip, sacroiliac joint, and/or TMJ, presence of erosive disease or enthesitis, delay in diagnosis, elevated levels of inflammation markers, symmetric disease) is conditionally recommended to guide treatment decisions.

Use of validated disease activity measures is conditionally recommended to guide treatment decisions, especially to facilitate treat-to-target approaches.

Treatment for oligoarthritis can and should be modified based on the involvement of specific joints or disease features (39,40). This could include rapid escalation of treatment (e.g., if there is TMJ involvement or erosive disease at presentation) or alternative medication choice (e.g., sulfasalazine or bDMARD rather than methotrexate for sacroiliitis) (3).

Voting panelists conditionally recommended formal assessment of disease activity using validated measures. There are several validated disease activity measures for childhood arthritis (41). The lack of demonstrated superiority of specific measures and the likelihood of future changes led voting panelists to defer stating formal preferences for particular measures. Measures that can be considered include Wallace preliminary criteria for Clinical Remission, ACR provisional criteria for inactive disease, Juvenile Arthritis Disease Activity Score (JADAS), and clinical JADAS, among others (42–46).

Treat-to-target approaches have been strongly endorsed for polyarticular JIA (47), and preliminary data have demonstrated feasibility as well as improved outcomes (48,49). Despite the limited number of studies in oligoarticular disease, one would expect a similar response. Presence of risk factors for poor outcomes may justify rapid escalation of treatment.



DMARD = disease-modifying antirheumatic drug, JIA = juvenile idiopathic arthritis, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal antiinflammatory drugs, TMJ = temporomandibular joint

Figure 2. Treatment algorithm for temporomandibular joint arthritis.

Active TMJ arthritis (Figure 2 and Table 4)

TMJ disease may be isolated or part of generalized arthritis. Treatment of TMJ arthritis is critical, as patients/caregivers noted high impact on oral health–related quality of life and challenges with diagnosis and effective pharmacologic treatment (50,51). In this guideline, therefore, treatment of TMJ arthritis is recommended regardless of presence of clinical symptoms. While NSAIDs and/or IAGCs may be sufficient treatment for some patients, rapid escalation to bDMARDs (potentially in combination with csDMARDs) is often appropriate despite limited evidence, given the impact and destructive nature of TMJ arthritis (52).

NSAIDs

A trial of scheduled NSAIDs is conditionally recommended as part of initial therapy for active TMJ arthritis.

NSAIDs have long been the cornerstone of treatment for JIA and can ease discomfort (11). However, the initial NSAID trial should be brief due to potential adverse effects (e.g., gastritis, bruising) and limited efficacy (unless inactive disease is achieved). Voting panelists could not agree on the appropriate duration of initial use before escalating therapy, as some panelists prefer that the use of NSAIDs be avoided altogether.

Glucocorticoids

IAGCs are conditionally recommended as part of initial therapy for active TMJ arthritis.

There is no preferred agent.

IAGCs may alleviate joint symptoms and help restore function. This recommendation is conditional, as there have been unique TMJ-specific serious adverse events, including heterotopic ossification and impaired growth (52–55). Therefore, IAGCs for TMJ arthritis should be used sparingly for symptomatic children, preferably those who are skeletally mature (53–56). There are no comparative data between different IAGC formulations for TMJ injections.

Oral glucocorticoids are conditionally recommended *against* as part of initial therapy for active TMJ arthritis.

If, despite recommendations against, oral glucocorticoids are given to quickly alleviate severe symptoms prior to the onset

Table 4. TMJ arthritis*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
A trial of scheduled NSAIDs is **conditionally** recommended as part of initial therapy.	Very low	PICO 11. In children with JIA with active TMJ arthritis, should a trial of scheduled NSAIDs be recommended, and should there be any preferred NSAID treatment?	53
IAGCs are **conditionally** recommended as part of initial therapy.	Very low	PICO 12. In children with JIA with active TMJ arthritis, should adding intraarticular glucocorticoids to initial therapy be recommended?	53–57
There is no preferred agent.	Very low	PICO 14. In children with JIA with active TMJ arthritis, should a specific steroid type be recommended for intraarticular injection?	58
Oral glucocorticoids are **conditionally** recommended *against* as part of initial therapy.	Very low	PICO 13. In children with JIA with active TMJ arthritis, should adding oral glucocorticoids to initial therapy be recommended?	58
Conventional synthetic DMARDs are **strongly** recommended for inadequate response to or intolerance of NSAIDs and/or IAGCs. MTX is **conditionally** recommended as a preferred agent over LEF.	Very low	PICO 15. In children with JIA with active TMJ arthritis, should DMARD therapies be recommended, and should there be any preferred order of treatment: MTX (subcutaneous and oral), LEF, SSZ, and/or HCQ?	58–59
Biologic DMARDs are **conditionally** recommended for inadequate response to or intolerance of NSAIDs and/or IAGCs and at least 1 conventional synthetic DMARD. There is no preferred biologic agent.	Very low	PICO 16. In children with JIA with active TMJ arthritis, should systemic biologic therapies be recommended, and should there be any preferred order of treatment: TNFi, biologic treatments with other mechanisms of action?	59
Consideration of poor prognostic features (e.g., involvement of ankle, wrist, hip, sacroiliac joint, and/or TMJ, presence of erosive disease or enthesitis, delay in diagnosis, elevated levels of inflammation markers, symmetric disease) is **conditionally** recommended to guide treatment decisions.	Very low	PICO 19. In children with JIA with active TMJ arthritis, should poor prognostic features alter the treatment paradigm?	60

* TMJ = temporomandibular joint; PICO = Patient/Population, Intervention, Comparison, and Outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; JIA = juvenile idiopathic arthritis; IAGCs = intraarticular glucocorticoids; DMARDs = disease-modifying antirheumatic drugs; MTX = methotrexate; LEF = leflunomide; SSZ = sulfasalazine; HCQ = hydroxychloroquine; TNFi = tumor necrosis factor inhibitor.
† In Supplementary Appendix 3, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42037/abstract.

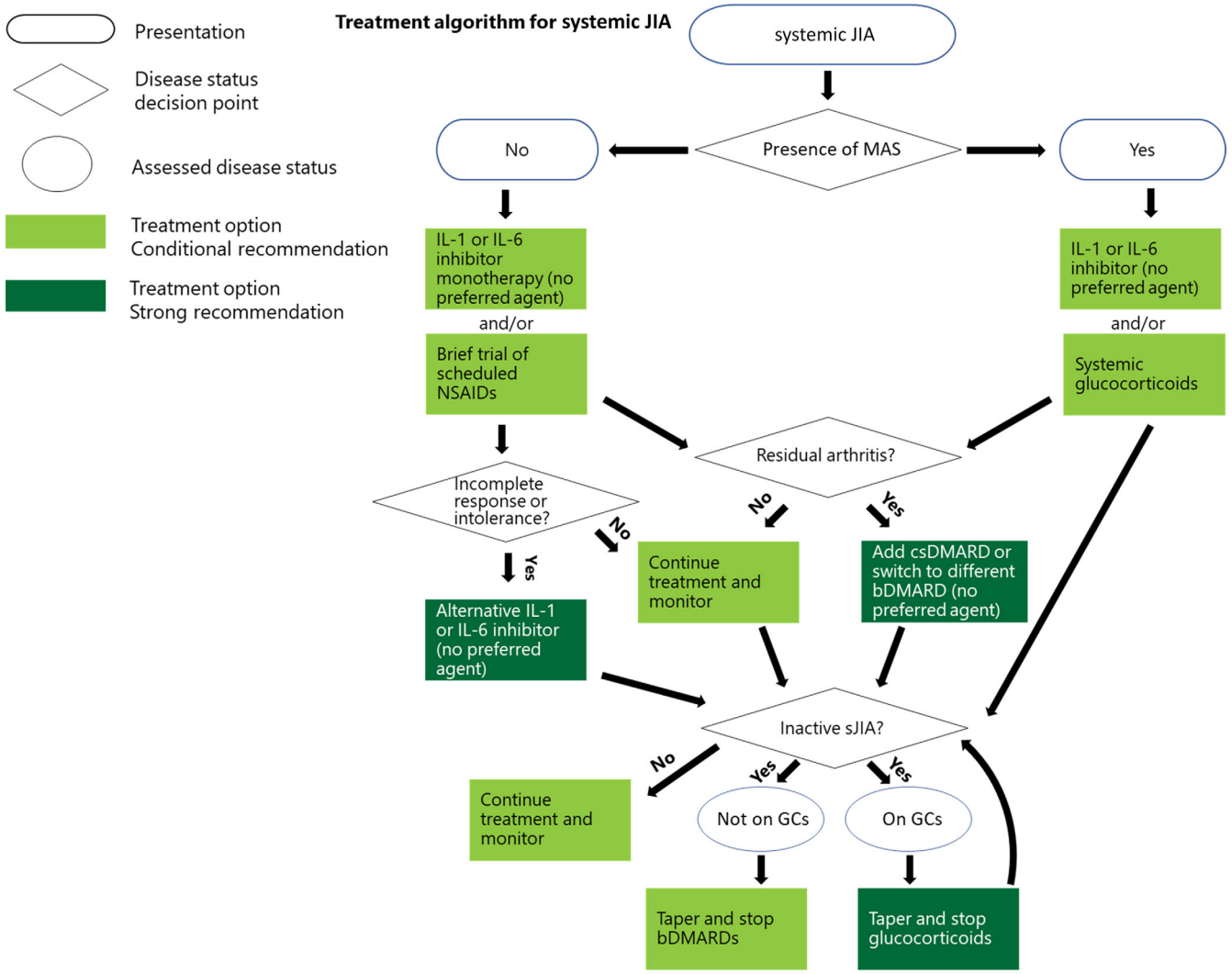
of action of DMARDs, treatment should be limited to the lowest effective dose for the shortest duration possible (20).

Conventional synthetic DMARDs

Conventional synthetic DMARDs are strongly recommended for inadequate response to or intolerance of NSAIDs and/or IAGCs for active TMJ arthritis.

Methotrexate is conditionally recommended as a preferred agent over leflunomide.

The TMJ is a high-risk joint due to major impact on activities of daily living, and thus, early use of csDMARD therapy is encouraged. The limited available evidence supports the use of methotrexate (57). However, because not all patients tolerate methotrexate well, leflunomide is recommended as an alternative, if needed.



bDMARD = biologic disease-modifying antirheumatic drug, csDMARD = conventional synthetic disease-modifying antirheumatic drug, GCs = glucocorticoids, IL = interleukin, JIA = juvenile idiopathic arthritis, MAS = macrophage activation syndrome, NSAIDs = nonsteroidal antiinflammatory drugs

Figure 3. Treatment algorithm for systemic juvenile idiopathic arthritis.

Biologic DMARDs

Biologic DMARDs are conditionally recommended for inadequate response to or intolerance of NSAIDs and/or IAGCs and at least 1 csDMARD for active TMJ arthritis.

There is no preferred bDMARD.

Voting panelists deferred recommending a specific bDMARD because current studies of TMJ arthritis have been small and observational (52,58). TNFi treatment has been most commonly used. As noted above, the use of IL-1 inhibitors is restricted to the treatment of systemic JIA.

Systemic JIA with and without MAS (Figure 3)

Systemic JIA is distinct from all other categories of JIA due to fever, rash, and visceral involvement and is considered by some to be an autoinflammatory disorder (59). Disease pathogenesis and cytokine involvement in systemic JIA are different than in other JIA categories (60–62). Up to 40% of cases of systemic JIA are associated with MAS, a secondary hemophagocytic syndrome that is a life-threatening complication requiring urgent recognition and treatment. MAS presents with fevers, high ferritin levels, cytopenias, elevated liver enzyme levels, low fibrinogen levels, and high triglyceride levels (63,64). As it may occur at any point during the disease course, careful monitoring is necessary for children with or without MAS at presentation.

Systemic JIA without MAS: initial therapy (Table 5)

Biologic DMARDs

Biologic DMARDS (IL-1 and IL-6 inhibitors) are conditionally recommended as initial monotherapy for systemic JIA without MAS.

Table 5. Systemic JIA without MAS*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
NSAIDs are **conditionally** recommended as initial monotherapy. Oral glucocorticoids are **conditionally** recommended *against* as initial monotherapy.	Very low	PICO 20. In patients with treatment-naive, newly diagnosed systemic JIA without MAS, should non-DMARD treatment (NSAIDs, glucocorticoids) be used as initial therapy?	61–67
Conventional synthetic DMARDs are **strongly** recommended *against* as initial monotherapy.	Very low	PICO 21. In patients with treatment-naive, newly diagnosed systemic JIA without MAS, should DMARD treatment (MTX, calcineurin inhibitor) be used as initial therapy, and is there a preferred order?	67–68
Biologic DMARDs (IL-1 and IL-6 inhibitors) are **conditionally** recommended as initial monotherapy. There is no preferred agent.	Very low	PICO 22. In patients with treatment-naive, newly diagnosed systemic JIA without MAS, should biologic treatment (anakinra, canakinumab, tocilizumab, or others) be used as initial therapy, and is there a preferred order?	69–71
IL-1 and IL-6 inhibitors are **strongly** recommended over a single or combination of conventional synthetic DMARDs for inadequate response to or intolerance of NSAIDs and/or glucocorticoids.	Very low	PICO 23. In patients with systemic JIA without MAS who do not respond to initial therapy with nonbiologic treatments (NSAIDs, glucocorticoids, DMARDs), should nonbiologic treatments be combined or biologic treatment started?	72–130
Biologic DMARDs or conventional synthetic DMARDs are strongly recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors. There is no preferred agent.	Very low	PICO 27. In patients with systemic JIA in whom inactive disease is not achieved despite treatment with both IL-1 and IL-6 agents and/or who are chronically steroid dependent, is long-term stable steroid treatment superior to nonsteroid treatments (cyclophosphamide or abatacept or rituximab or IVIG or mesenchymal stem cell transplant or bone marrow transplant) for achievement of inactive disease, achievement of partial response, growth, ability to taper/discontinue steroids, and minimization of side effects/medication toxicity?	138

* JIA = juvenile idiopathic arthritis; MAS = macrophage activation syndrome; PICO = Patient/Population, Intervention, Comparison, and Outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; IL-1 = interleukin-1; IVIG = intravenous immunoglobulin.
† In Supplementary Appendix 3, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42037/abstract.

There is no preferred agent.

IL-1 and IL-6 inhibitors are extremely effective and well-tolerated treatments for systemic JIA (60–62) and have been rapidly adopted in clinical practice (65,66). Use of IL-1 and IL-6 inhibitors to treat systemic JIA has allowed for marked reduction in glucocorticoid use (60,61,67). Patients/caregivers agreed with this recommendation, given historical delays and limits in clinical response and toxicities from other medications before the bDMARD era.

Some voting panelists preferred starting with a short-acting agent such as anakinra, but in the absence of controlled studies, no preferred agent was endorsed. Patients/caregivers noted preference for fewer injections, if possible. As response to individual agents is variable, switching among and between IL-1 and IL-6 inhibitors when needed due to lack of efficacy or poor tolerability is appropriate.

Concerns were expressed regarding a highly fatal lung disease observed in some children with systemic JIA, most of whom were treated with bDMARDs. Observed risk factors include younger age with MAS, a history of reactions to tocilizumab, and trisomy 21 (68,69). The exact etiology of systemic JIA–associated lung disease and recommendations for screening remain under

Table 6. Systemic JIA with MAS*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
Formal recommendation deferred	Very low	PICO 24. In patients with systemic JIA, does the presence of subclinical MAS alter the treatment paradigm?	130
IL-1 and IL-6 inhibitors are **conditionally** recommended over calcineurin inhibitors alone to achieve inactive disease and resolution of MAS. Glucocorticoids are **conditionally** recommended as part of initial treatment of systemic JIA with MAS. There is no preferred agent.	Very low	PICO 25. In patients with systemic JIA and overt MAS, is biologic therapy superior to calcineurin inhibitors for achievement of inactive disease and resolution of MAS?	131–136
Formal recommendation deferred	Very low	PICO 26. For nonresponse or partial response to biologic therapy, is addition of a calcineurin inhibitor superior to etoposide or IVIG or plasmapheresis for achievement of inactive disease and resolution of MAS?	137–138
Biologic DMARDs or conventional synthetic DMARDs are **strongly** recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors. There is no preferred agent.	Very low	PICO 27. In patients with systemic JIA in whom inactive disease is not achieved despite treatment with both IL-1 and IL-6 agents and/or who are chronically steroid dependent, is long-term stable steroid treatment superior to nonsteroid treatments (cyclophosphamide or abatacept or rituximab or IVIG or mesenchymal stem cell transplant or bone marrow transplant) for achievement of inactive disease, achievement of partial response, growth, ability to taper/discontinue steroids, and minimization of side effects/medication toxicity?	138

* JIA = juvenile idiopathic arthritis; MAS = macrophage activation syndrome; PICO = Patient/Population, Intervention, Comparison, and Outcomes; IL-1 = interleukin-1; IVIG = intravenous immunoglobulin; DMARDs = disease-modifying antirheumatic drugs.
† In Supplementary Appendix 3, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42037/abstract.

investigation. Affected children often present with acute digital clubbing, which should raise immediate concern (68,69). However, voting panelists noted the need to balance the effectiveness and relative safety of bDMARDs with the rarity of this serious outcome. Voting panelists were also motivated by the extent of morbidity from undertreated systemic JIA and glucocorticoid-associated toxicities before the bDMARD era (70,71).

NSAIDs

NSAIDs are conditionally recommended as initial monotherapy for systemic JIA without MAS.

Studies suggest that a small proportion of patients with systemic JIA will respond to NSAIDs alone (72). Patients/caregivers agreed with a short trial of NSAIDs for those children. If clinical response is not rapid and complete, rapid escalation of therapy is recommended. Voting panelists could not agree on the appropriate duration of initial use before escalating therapy, as many panelists prefer that the use of NSAIDs be avoided altogether for systemic JIA.

Glucocorticoids

Oral glucocorticoids are conditionally recommended *against* as initial monotherapy for systemic JIA without MAS.

In most cases, oral glucocorticoids should not be used as initial monotherapy in patients with systemic JIA without MAS and, if used, should be limited to the lowest effective dosage for the shortest duration possible. This recommendation is conditional, as bDMARDs may not always be immediately available, and glucocorticoids may help control systemic and joint manifestations until IL-1 or IL-6 inhibitors can be started.

Table 7. Systemic JIA with inactive disease*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
Tapering and discontinuing glucocorticoids is **strongly** recommended after inactive disease has been attained.	Very low	PICO 28. In patients with systemic JIA with inactive disease treated with oral steroids, is taper to discontinuation of steroids superior to continuing long-term stable-dose steroids for preventing disease flare and minimizing side effects/medication toxicity?	139
Tapering and discontinuing biologic DMARDs is **conditionally** recommended after inactive disease has been attained.	Very low	PICO 29. In patients with systemic JIA in clinical remission with biologic monotherapy, is tapering by decreasing dosage superior to tapering dosing interval at preventing disease exacerbation, preventing development of antidrug antibodies, and minimizing medication toxicity?	140–143

* JIA = juvenile idiopathic arthritis; PICO = Patient/Population, Intervention, Comparison, and Outcomes; DMARDs = disease-modifying antirheumatic drugs.
† In Supplementary Appendix 3, on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42037/abstract.

Conventional synthetic DMARDs

Conventional synthetic DMARDs are strongly recommended *against* as initial monotherapy for systemic JIA without MAS.

This recommendation is strong despite limited evidence, as the Voting Panel noted multiple small studies of systemic JIA that documented lack of efficacy at controlling systemic features that are typically present at onset of disease, leading to a continued need for glucocorticoids (66,73). Conventional synthetic DMARDs in combination with bDMARDs can be considered for children with prominent arthritis (74). In areas where biologic therapy is not rapidly attainable, thalidomide has been used to treat systemic JIA (75). However, given ready bDMARD availability in North America and risks of thalidomide toxicity, use of thalidomide was not considered as part of this guideline.

Systemic JIA without MAS: subsequent therapy (Table 5)

IL-1 and IL-6 inhibitors are strongly recommended over a single or combination of csDMARDs for inadequate response to or intolerance of NSAIDs and/or glucocorticoids for systemic JIA without MAS.

Most physicians and patients/caregivers preferred quickly starting IL-1 or IL-6 inhibitors for insufficient response to NSAIDs or glucocorticoids (66). Panel members were persuaded by trials that documented resolution of systemic signs and ability to discontinue glucocorticoids (60,76–78).

Biologic DMARDs or conventional synthetic DMARDs are strongly recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors.

There is no preferred agent.

Given the potential toxicities from long-term use of glucocorticoids (20), patients should receive steroid-sparing treatments for residual arthritis. There are many options (e.g., adding methotrexate, switching to abatacept or a TNFi), and ample evidence supports the use of DMARDs for systemic JIA–associated synovitis (23,79).

Systemic JIA with MAS: initial therapy (Table 6)

Infections can trigger MAS; therefore, all persons with MAS should be evaluated for infection concurrently with or prior to initiation of therapy (80,81).

Biologic DMARDs

IL-1 or IL-6 inhibitors are conditionally recommended over calcineurin inhibitors alone to achieve inactive disease and resolution of MAS for systemic JIA with MAS.

There is no preferred agent.

IL-1 and IL-6 inhibitors have proven to be very helpful in the treatment of systemic JIA and MAS (82–84). Some voting panelists noted that monotherapy may not be sufficient for severely ill patients (83). Biologic DMARDs combined with glucocorticoids and calcineurin inhibitors may be necessary to control MAS in some patients (85).

Glucocorticoids

Glucocorticoids are conditionally recommended as part of initial treatment of systemic JIA with MAS.

The benefits of glucocorticoids for MAS often outweigh their risks, even in patients whose MAS is triggered by infection. Systemic glucocorticoids may be necessary for severely ill patients

because they can have a rapid onset of action. However, although treatment with high-dose glucocorticoids may be required for disease control, subsequent glucocorticoid therapy should be limited to the lowest effective dosage for the shortest duration possible. Longer-term glucocorticoid therapy in children is not appropriate because of its effects on bone health and growth (20).

Systemic JIA with MAS: subsequent therapy (Table 6)

Biologic DMARDS or csDMARDs are strongly recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors.

Inactive systemic JIA with or without history of MAS (Table 7)

Tapering and discontinuing glucocorticoids is strongly recommended after inactive disease has been attained in systemic JIA.

The risk of flare from systemic JIA that is well controlled is considerably outweighed by possible harms from long-term glucocorticoid use, even at low doses (86), accounting for this strong recommendation. If a patient is receiving both DMARDs and glucocorticoids, systemic glucocorticoids should be tapered and discontinued first before attempting to taper bDMARDs or csDMARDs. It is unclear how soon or rapidly these can be safely discontinued in patients with inactive systemic JIA.

Tapering and discontinuing bDMARDs is conditionally recommended after inactive disease has been attained in systemic JIA.

In children with systemic JIA whose disease is inactive, it may be possible to maintain this inactive disease state with lower doses of, or discontinuation of, bDMARDs (74,87). It is unclear how soon after achievement of inactive disease these can be tapered. No method of tapering is specified (e.g., decreasing dosage versus increasing intervals between doses) given lack of evidence (86), but patients/caregivers tended to prefer increasing intervals.

DISCUSSION

The recommendations presented herein are a companion to those published in 2019 (3,4) and cover areas not previously addressed: oligoarthritis, TMJ arthritis, and systemic JIA with and without MAS. In many ways, one must view this guideline as a road map for future study. Most of the available evidence for the relevant PICO questions was of very low quality, contributing to 16 of the 25 recommendations being conditional. None of the recommendations were supported by moderate- or high-quality evidence. Similar to the 2019 guidelines, recommendations are grouped based on disease phenotype and not by specific classification criteria, reflecting clinical practice, in which disease characteristics, severity, and risk of damage generally drive treatment decisions. These recommendations differ quite substantially from those published in 2011 and 2013 (1,2), reflecting increased experience with and availability of bDMARDs as well as a deeper understanding of JIA pathogenesis and long-term risks of undertreatment.

The Voting Panel and Patient/Caregiver Panel both engaged in vigorous discussions over the use of NSAIDs and oral glucocorticoids (88) in the treatment of JIA, regardless of phenotype. Given the availability of safer, effective alternatives, both panels agreed that these medications should be used sparingly and largely as a bridge until more definitive treatment is available. This is a marked change from previous clinical practice, in which both were mainstays of treatment and subsequent risk of chronic disability was high (89,90).

Another major change in recommendations for the treatment of systemic JIA is the use of bDMARDs as initial treatment or upon inadequate response to a short course of NSAIDs. The addition of csDMARDs is recommended only for persistent synovitis despite treatment with bDMARDs. This recommendation reflects growing understanding about the roles of specific cytokines in systemic JIA and the ability to induce remission with targeted therapy against IL-6 and IL-1 (62,74,91). Reports of a highly fatal lung disease in some bDMARD-treated young children with systemic JIA (68,69) temper this enthusiasm, and additional investigation is needed to determine what role, if any, bDMARDs play in the pathogenesis of this complication.

This guideline's focus on oligoarthritis complements previously published recommendations for polyarthritis (3). However, it was clear in Voting Panel discussions that the number of involved joints alone was insufficient to tailor treatment decisions. Specific involvement of key joints (e.g., TMJ, wrist, sacroiliac, hip, and ankle) and other features (e.g., erosions) were considered reasonable justification for early escalation of therapy (92). This approach is reflected in a distinct set of recommendations specifically addressing TMJ arthritis.

The use of IAGCs was extensively discussed. Recommendations from 2011 and 2019 to preferentially use triamcinolone hexacetonide for oligoarthritis (1,3) were reaffirmed, while no specific formulation for TMJ IAGC injection was noted. Triamcinolone hexacetonide has been shown to be superior to alternative injectable glucocorticoids in achieving and maintaining remission in children with JIA (17–19). Triamcinolone hexacetonide has been commercially unavailable in the US for many years, forcing physicians to consider less effective, more toxic, or more costly alternatives. However, very recently the FDA allowed the importation of one particular formulation of triamcinolone hexacetonide specifically for joint injections in patients with JIA (93) to address an identified unmet medical need.

There is much that remains to be learned. Studies must be performed to obtain high-quality data to fill in the evidentiary gaps (Supplementary Appendix 7, available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/

10.1002/art.42037/abstract). There remain important areas with little or no evidence to guide management, suggesting an agenda for future research. Head-to-head trials are needed to understand the optimal order and roles of csDMARDs and bDMARDs for children with JIA. We need improved understanding of which class of medication is best for a particular child, allowing for more precise treatment and less time before remission is attained. Biosimilars were not addressed in this guideline, as these medications were not included in the literature review, and there was no available evidence assessing their use in JIA. More widespread use of biosimilars will add more questions about their relative safety and effectiveness in children who start or switch to them for JIA treatment.

Patient/caregiver input was instrumental in creating these recommendations. Several major themes emerged from their participation. Patients/caregivers stressed the need for individualizing treatments because what works for one does not work for all (94). To facilitate individualization, no rigid time frames were required for an advancement of treatment. Moving quickly may be needed for a patient whose condition is rapidly worsening, while moving more slowly may be appropriate for one whose condition has improved substantially but not fully. Panel participants emphasized the critical importance of shared decision-making that considers patients' and caregivers' values, goals, and preferences (95). The depth and breadth of the impact of JIA on the lives and well-being of affected children and their families cannot be overstated (96,97). It is hoped that in the future, more effective, reliable treatments for this disease will be available (98).

This guideline breaks new ground in recommending treatment withdrawal for children with systemic JIA, who may have lower risks of flare than are associated with other forms of JIA (99,100). As we look toward the future, we can only hope that similar recommendations around tapering medications can be made for every JIA category. There is a need for biomarkers that can help distinguish disease that still requires treatment from that which has completely resolved, as currently the risk of relapse remains high upon medication tapering.

The low quality of evidence supporting these recommendations underscores the importance of clinical judgment and shared decision-making in everyday care of individuals with JIA. Similarly, this guideline and the many uncertainties acknowledged herein represent a powerful reminder of the need for more high-quality evidence to support (or refute) current practices and to improve the management of JIA and well-being of all individuals living with the disease.

ACKNOWLEDGMENTS

We thank Jennifer Horonjeff who (along with author Katherine Murphy) participated in the Patient Panel meeting. We thank the ACR staff, including Regina Parker for assistance in coordinating the administrative aspects of the project and Cindy Force for assistance with manuscript preparation. We thank Janet Waters for assistance in developing the literature search strategy as well as performing the initial literature search and update searches.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Onel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Arthritis & Rheumatology
Vol. 73, No. 11, November 2021, pp 1966–1975
DOI 10.1002/art.41879
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American College of Rheumatology
Empowering Rheumatology Professionals

Definition and Validation of the American College of Rheumatology 2021 Juvenile Arthritis Disease Activity Score Cutoffs for Disease Activity States in Juvenile Idiopathic Arthritis

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This work has been approved by the American College of Rheumatology (ACR) Board of Directors. This signifies that it has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR-approved criteria sets are expected to undergo intermittent updates. The ACR is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.

Objective. To develop and validate new Juvenile Arthritis Disease Activity Score 10 (JADAS10) and clinical JADAS10 (cJADAS10) cutoffs to separate the states of inactive disease (ID), minimal disease activity (MiDA), moderate disease activity (MoDA), and high disease activity (HDA) in children with oligoarthritis and with rheumatoid factor–negative polyarthritis, based on subjective disease assessment by the treating pediatric rheumatologist.

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Dr. Nikishina has received consulting fees, speaking fees, and/or honoraria from Novartis, MSD, Pfizer, AbbVie, Hoffmann-La Roche, and Janssen (less than $10,000 each). Dr. Avcin has received consulting fees, speaking fees, and/or honoraria from AbbVie, Octapharma, Takeda, and Alexion (less than $10,000 each). Dr. Quartier has received consulting fees, speaking fees, and/or honoraria from AbbVie, Bristol Myers Squibb, Chugai-Roche, Lilly, Novartis, NovImmune, and Sobi (less than $10,000 each). Dr. Ringold has received salary support from the Childhood Arthritis and Rheumatology Research Alliance. Dr. Ruperto has received consulting fees, speaking fees, and/or honoraria from Ablynx, AstraZeneca-Medimmune, Bayer, Biogen, Boehringer, Bristol Myers Squibb, Celgene, Eli Lilly, EMD Serono, GlaxoSmithKline, Hoffmann-La Roche, Janssen, Merck, Novartis, Pfizer, R/Pharma, Sinergie, Sobi, and UCB (less than $10,000 each). Dr. Ravelli has received consulting fees, speaking fees, and/or honoraria from AbbVie, Angelini, Bristol Myers Squibb, Pfizer, Hoffmann-La Roche, Novartis, Pfizer, and Reckitt Benckiser (less than $10,000 each). Dr. Consolaro has received speaking fees from AbbVie and Pfizer (less than $10,000 each) and research grants from Pfizer and Alfasigma. No other disclosures relevant to this article were reported.

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Submitted for publication January 26, 2021; accepted in revised form May 18, 2021.

Methods. The cutoffs definition cohort was composed of 1,936 patients included in the multinational Epidemiology, Treatment and Outcome of Childhood Arthritis (EPOCA) study. Using the subjective physician rating as an external criterion, 4 methods were applied to identify the cutoffs: mapping, Youden index, 90% specificity, and maximum agreement. The validation cohort included 4,014 EPOCA patients, patients from 2 randomized trials, and 88 patients from the PharmaChild registry. Cutoff validation was conducted by assessing discriminative and predictive ability.

Results. The JADAS10 cutoffs were 1.4, 4, and 13, respectively, for oligoarthritis and 2.7, 6, and 17, respectively, for polyarthritis. The cJADAS10 cutoffs were 1.1, 4, and 12, respectively, for oligoarthritis and 2.5, 5, and 16, respectively, for polyarthritis. The cutoffs discriminated strongly among different levels of pain and morning stiffness, between patients who were and those who were not prescribed a new medication, and between different levels of improvement in clinical trials. Achievement of ID and MiDA according to the new JADAS cutoffs at least twice in the first year of disease predicted better outcome at 2 years.

Conclusion. The 2021 JADAS and cJADAS cutoffs revealed good metrologic properties in both definition and validation samples, and are therefore suitable for use in clinical trials and routine practice.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease with a widely variable clinical course and outcome (1). Persistently active disease and uncontrolled synovial inflammation may cause structural joint damage (2), which may in turn lead to serious impairment of physical function and have marked impact on the quality of life of children and their families (3,4). Thus, regular assessment of the level of disease activity in children with JIA is fundamental to monitor the course of the disease over time and the effectiveness of therapeutic interventions. A precise measurement of disease activity may also have prognostic implications. For instance, achievement of the state of inactive disease (ID) at least once in the first 5 years was found to be associated with lower levels of long-term damage and functional impairment (5). Furthermore, the time spent in the state of active disease in the first 2 years was the most significant factor associated with the duration of active disease over the following years (6).

In the last decade, the use of composite disease activity scores in JIA has gained increasing popularity. These tools enable an easy and pragmatic approach to the quantification of disease activity by providing a summary number on a continuous scale, which is calculated by calculating the simple arithmetic sum of the scores of their individual components. The first composite disease activity score for JIA was developed in 2009 and was named the Juvenile Arthritis Disease Activity Score (JADAS) (7). The JADAS includes the following 4 measures: physician global assessment of disease activity measured on a 0–10 visual analog scale (VAS), parent/patient global assessment of child well-being measured on a 0–10 VAS, count of joints with active disease among the total assessed (10, 27, or 71 joints depending on the version), and the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level (8), both normalized to a 0–10 scale. A simplified, 3-item version of the score called the clinical JADAS (cJADAS), which excludes the acute-phase reactants, was subsequently published (9). Among the different versions of the score, the JADAS10 and the cJADAS10 have been more widely adopted as they are simpler than and equally effective as the other versions.

Proper interpretation of the scores obtained with JADAS calculation requires the definition of criteria for identifying high and low levels of disease activity (10). Cutoff values to separate the states of ID, minimal disease activity (MiDA), moderate disease activity (MoDA), and high disease activity (HDA) were established for both the JADAS (11,12) and the cJADAS (13). These cutoffs were defined with reference to published criteria for clinically inactive disease (CID) (14) and MiDA (15). At the time of previous cutoff definition, these criteria were considered as the only available external reference. However, use of these criteria has some limitations. The published criteria for CID include 3 of the 4 items in the JADAS, all of which must be scored zero. Thus, the variability of the JADAS in a patient who meets the criteria for CID can only be due to the fourth component, i.e., the parent/patient global assessment of the child's well-being. Similar concerns could be raised with regard to the definition of MiDA and the related JADAS cutoffs. Previous cutoffs for HDA were based on the treatment choices made by the treating physician. Potential limitations of the latter approach are that therapeutic choices may be driven by factors other than disease activity and that therapeutic decisions may vary across pediatric rheumatologists practicing in diverse geographic settings or with different clinical experience.

In a recently completed project (16), a large multinational cohort of JIA patients was enrolled and data collected on the treating physician's subjective rating of disease activity. In the present study, we took advantage of this large data set to develop and test new JADAS10 and cJADAS10 cutoffs for oligoarthritis and rheumatoid factor (RF)–negative polyarthritis disease activity states based on the subjective perception of international pediatric rheumatologists.

PATIENTS AND METHODS

Patient population used for the development of JADAS cutoffs. The cutoff definition cohort was selected from among the consecutive JIA patients included in the multinational Epidemiology, Treatment and Outcome of Childhood Arthritis (EPOCA) study (16), whose aims were to investigate the prevalence of JIA categories in different geographic areas, to gain

information on the treatments prescribed by international pediatric rheumatologists, and to assess the disease and health status of children with JIA living in diverse parts of the world. The EPOCA study included 9,081 patients enrolled in 49 countries between April 4, 2011 and November 21, 2016. For the purpose of the study, each JIA patient underwent a cross-sectional visit, during which the treating physician was asked to subjectively rate the disease status as ID, MiDA, MoDA, or HDA.

The oligoarthritis cutoff definition cohort consisted of the patients enrolled at the 20 centers that provided the largest sample of patients with persistent oligoarthritis. The number of oligoarthritis patients in each center ranged from 35 to 65. The polyarthritis cutoff definition cohort consisted of the patients enrolled at the 20 centers that provided the largest sample of patients with extended oligoarthritis and RF-negative polyarthritis. The number of polyarthritis patients in each center ranged from 35 to 65.

Patient populations used for the validation of JADAS cutoffs. Patients in the EPOCA study who had oligoarthritis or polyarthritis according to the International League of Associations for Rheumatology categorization (17) (subclassified as above) and who were not part of the cutoff definition cohort were included in the cutoff validation cohort. In addition, we obtained longitudinal data from 2 randomized clinical trials. The first (the TRIMECA trial [Comparison of the Efficacy of Intraarticular Corticosteroid Therapy Administered Alone or in Combination with Methotrexate in Children with JIA]) was a multicenter randomized clinical trial conducted in Italy between July 7, 2009 and March 31, 2013, which compared intraarticular glucocorticoid injections alone versus intraarticular glucocorticoid injections plus methotrexate in the treatment of oligoarticular JIA in a study population of 207 patients (18). The second was a randomized controlled trial conducted between February 2004 and June 2006, which assessed the efficacy and safety of abatacept withdrawal versus continuation in 190 patients with JIA (19). In the latter data set, only patients with extended oligoarticular arthritis and RF-negative polyarthritis were considered for cutoff validation.

To assess predictive ability, a fourth sample of patients was obtained from PharmaChild (20), a multinational registry to assess the long-term safety and efficacy of medications in children with JIA. We included all patients who had undergone at least 4 prospective visits in the first year of observation and a complete clinical assessment at 2 years after enrollment.

Methods used to calculate the cutoffs. The methodology for the definition of rheumatoid arthritis disease activity states based on the Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI) (10) was adapted for the present study. The following 4 methods were used to identify cutoffs in the JADAS10 and cJADAS10 to distinguish the states of ID, MiDA, MoDA, and HDA in oligoarthritis and RF-negative polyarthritis: mapping, Youden index, 90% specificity, and agreement. The median of the values obtained with the 4 methods was retained as the cutoff for each disease activity state. For these analyses, we used the OptimalCutpoints package for R statistics, version 3.3.3 (21). This application computes optimal cut points for diagnostic tests or continuous markers and allows for selection of different approaches.

Mapping. For definition of the cutoff separating the states of ID and MiDA, the 75th percentile values of the JADAS10 and cJADAS10 in patients judged by their treating physician as having ID were retained. For definition of the cutoff separating the states of MiDA and MoDA, the 75th percentile values of the JADAS10 and cJADAS10 in patients judged as having ID or MiDA were retained. For definition of the cutoff separating the states of MoDA and HDA, the 25th percentile values of the JADAS10 and cJADAS10 in patients judged by their treating physician as having HDA were retained. Since for this analysis we considered it important to assign the same weight to each center regardless of the number of patients studied at the center, the cutoff values were retained separately for each center. The 20 values obtained for each cutoff were then averaged.

Youden index. The Youden index (J) identifies the maximum potential effectiveness of a biomarker through receiver operating characteristic (ROC) curve analysis. It is calculated with the formula $J = \max_c = (Se_c + Sp_c - 1)$, where $\max_c$ is the maximally effective cutoff, Se_c is the cutoff with the maximum sensitivity, and Sp_c is the cutoff with the maximum specificity. The cutoff that achieves this threshold is considered the best cutoff because it is the one that optimizes the discriminative ability of the evaluated parameter when sensitivity and specificity are weighted equally (22,23). For each of the 3 cutoffs, patients were divided into 2 mutually exclusive groups, coded as 0 or 1. For the cutoff separating ID from MiDA, the first group comprised patients judged as having ID by the attending physician and the second comprised patients judged as having MiDA, MoDA, or HDA; for the cutoff separating MiDA from MoDA, the first group comprised patients judged as having ID or MiDA and the second comprised patients judged as having MoDA or HDA; for the cutoff separating MoDA from HDA, the first group comprised patients judged as having ID, MiDA, or MoDA and the second comprised patients judged as having HDA.

Ninety percent fixed specificity. With the 90% fixed specificity method, the 3 values identifying the states of ID, MiDA, MoDA, and HDA were obtained by fixing the specificity at 90% in the ROC curve analysis and considering the attending physician rating as the gold standard. This approach was chosen to minimize the rate of misclassification of patients with moderate/high disease activity as having inactive disease (24,25).

Evaluation of agreement. The analysis of agreement was based on the kappa statistic, which assesses the agreement beyond chance between 2 dichotomous ratings, using OptimalCutpoints for R statistics. The first rating was obtained using all

Table 1. JADAS10 and cJADAS10 cutoff values for classification of disease activity in children with juvenile idiopathic arthritis (oligoarthritis or polyarthritis) according to 4 different methods for determining optimal cutoffs*

Diagnosis, disease state distinction, JADAS version	Method for optimal cutoff determination				Median#	Sensitivity of chosen cutoff value	Specificity of chosen cutoff value	AUC
	75th percentile†	Youden index‡	90% specificity§	Kappa¶				
Oligoarthritis								
ID to MiDA								
JADAS10	1.5	1.2	1.9	1.2	1.4	76.1	93.6	0.919
cJADAS10	1.2	1.0	1.5	1.0	1.1	79.5	92.9	0.922
MiDA to MoDA								
JADAS10	3.9	4.0	4.2	9.2	4.0	77.4	90.7	0.923
cJADAS10	3.4	4.0	3.5	6.5	4.0	80.5	87.0	0.924
MoDA to HDA								
JADAS10	14.4	12.5	10.5	18.0	13.0	83.3	95.9	0.974
cJADAS10	14.3	10.0	9.5	15.0	12.0	76.2	95.0	0.971
Polyarthritis								
ID to MiDA								
JADAS10	2.6	2.7	2.3	3.0	2.7	79.1	90.2	0.925
cJADAS10	2.5	2.5	2.0	3.0	2.5	81.0	89.0	0.924
MiDA to MoDA								
JADAS10	5.1	5.9	5.9	9.9	6.0	79.8	88.6	0.927
cJADAS10	5.0	5.0	5.0	7.5	5.0	76.0	92.2	0.924
MoDA to HDA								
JADAS10	18.9	11.0	12.5	21.0	17.0	82.6	93.3	0.961
cJADAS10	19.0	10.5	12.5	19.0	16.0	81.5	93.9	0.960

* JADAS10 = Juvenile Arthritis Disease Activity Score 10; cJADAS10 = clinical JADAS10; AUC = area under the receiver operating characteristic curve; ID = inactive disease; MiDA = minimal disease activity; MoDA = moderate disease activity; HDA = high disease activity.
† Cutoff according to the 75th percentile of the cumulative score distribution.
‡ Cutoff, according to the Youden index (22,23), that best distinguishes between patients divided into 2 mutually exclusive groups coded as 0 or 1.
§ Cutoff according to fixed 90% specificity.
¶ Cutoff with best agreement according to kappa analysis.
# Median value among tentative cutoffs and chosen cutoff value.

possible JADAS10 and cJADAS10 values as hypothetical test criteria. To obtain the second rating, the categorical ratings from each attending physician (ID, MiDA, MoDA, or HDA) were dichotomized and were coded as 0 or 1, using the same approach as in the Youden index analysis. The software calculates the cutoff value with the highest kappa statistic.

Analyses performed to validate the cutoffs. Cutoff validation was based on assessment of discriminative and predictive ability. We tested whether the disease activity states according to the new cutoffs could discriminate 1) between patients in a cross-sectional sample with differing levels of various health outcomes, and 2) among different levels of response to a new treatment in 2 randomized clinical trials. Then, we tested the ability of JADAS10 and cJADAS10 states in the first year to predict clinically inactive disease at 2 years.

Ability to discriminate between different health states. In the EPOCA study, the median and interquartile range (IQR) level of pain on a 0–10-cm VAS (0 = no pain; 10 = maximum possible pain), the median and IQR count of joints with restricted function, the median level of physical function measured with the Juvenile Arthritis Functional Ability Scale (26) (range 0–45, where 0 is normal physical function), the percentage of parents who reported being not satisfied with current disease outcome, the percentage of patients with morning stiffness lasting >15 minutes, and the percentage of patients who were prescribed a new therapy for JIA at the study visit were compared across disease activity states defined by JADAS10 and cJADAS10 cutoffs. It was predicted that the values of all the above parameters would increase progressively from ID to HDA, although the changes in physical function and count of joints with restricted function were expected to be less pronounced as these indicators are affected by both disease activity and damage. Quantitative measures were compared by Kruskal-Wallis test with Dunn's post hoc test. Percentages were compared by chi-square test, with Bonferroni correction used for post hoc analysis.

Ability to discriminate among different levels of improvement. Patients at the 4-month visit in the open-label portion of the abatacept trial and at the 3-month visit in the TRIMECA trial were divided, according to the level of the American College of Rheumatology (ACR) Pediatric (Pedi) response (27), into 6 mutually exclusive groups: nonresponders, and ACR Pedi 30, 50, 70, 90, and 100 responders. For each level of response, we calculated the proportion of patients with ID, MiDA, MoDA, and HDA according to the new JADAS cutoffs. We expected that the proportion of patients with ID, MiDA, and MoDA would increase and that the proportion of patients with HDA would decrease when a higher level of improvement was met (moving from nonresponders to ACR Pedi 100 responders). We also expected that in both trials a higher proportion of patients would have had JADAS10 and cJADAS10 scores above the cutoffs for HDA cutoffs at the baseline visit.

Ability to predict future disease outcome. Among subjects in the PharmaChild registry, we compared the median and IQR number of visits with JADAS10 and cJADAS10 scores below the cutoffs for ID and MiDA and above the cutoffs for HDA in the first year of observation between patients who were and those who were not categorized as having CID according to the 2011 ACR JIA criteria (14) at 2 years. We also compared, using the same end point, the percentage of patients who had and those who did not have 2 or more visits with ID, MiDA, or HDA in the first year of observation. We expected that patients whose disease was clinically inactive at 2 years according to the ACR JIA criteria would have a higher number of visits with ID or MiDA and a lower number of visits with HDA in the first year. The inclusion of the state of MoDA was not considered meaningful for this analysis, because it was not expected that the number of visits in this intermediate state could predict the disease outcome.

Comparison with 2012–2014 cutoffs. The analyses described above were repeated using cutoffs published in 2012–2014 (11–13), and the statistical performance of the older versus the newer set of criteria was compared for each analysis (see below). The complete results of comparative validation of 2012–2014 cutoffs are presented in the Supplementary Appendix,

Table 2. Disease activity states based on the JADAS10 and cJADAS10, according to 2021 cutoffs and 2012–2014 cutoffs*

	2021 cutoffs		2012–2014 cutoffs	
Disease activity state	JADAS10	cJADAS10	JADAS10	cJADAS10
Oligoarthritis				
Inactive disease	≤1.4	≤1.1	≤1	≤1
Minimal disease activity	1.5–4	1.2–4	1.1–2	1.1–1.5
Moderate disease activity	4.1–13	4.1–12	2.1–4.2	1.51–4
High disease activity	>13	>12	>4.2	>4
Polyarthritis				
Inactive disease	≤2.7	≤2.5	≤1	≤1
Minimal disease activity	2.8–6	2.6–5	1.1–3.8	1.1–2.5
Moderate disease activity	6.1–17	5.1–16	3.9–10.5	2.51–8.5
High disease activity	>17	>16	>10.5	>8.5

* JADAS10 = Juvenile Arthritis Disease Activity Score 10; cJADAS10 = clinical JADAS10.

available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41879/abstract.

RESULTS

Definition of cutoffs. The cutoff selection cohort comprised 979 patients with oligoarthritis and 957 patients with polyarthritis. Demographic and clinical features of the patients are shown in Supplementary Table 1, on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41879/abstract.

The JADAS10 and cJADAS10 cutoffs obtained with the 4 different statistical approaches and the final 3 cutoffs, calculated as the median of the 4 values to define the 4 disease states (ID, MiDA, MoDA, and HDA) in oligoarthritis and polyarthritis, are shown in Table 1. Table 2 presents the comparison of the current proposed cutoffs (2021 cutoffs) with cutoffs published in 2012–2014 (11–13). All of the 2021 cutoffs were higher than the 2012–2014 cutoffs.

Validation of cutoffs. *Ability to discriminate between different health states.* A total of 1,859 and 2,155 patients with oligoarthritis and polyarthritis, respectively, from the EPOCA study were included in this analysis; demographic and clinical features are shown in Supplementary Table 1. The level of pain increased progressively from ID through HDA in both patient groups, based on either JADAS10 or cJADAS10 cutoffs (Figure 1). Likewise, the count of joints with restricted function and the physical function score worsened progressively throughout the same states ($P < 0.001$). However, Dunn's post hoc test revealed that among patients with oligoarthritis, only pain and physical function were different between all 4 disease activity states ($P < 0.001$ for all comparisons), whereas the count of joints with restricted function did not differ between patients with ID and patients with MiDA ($P = 0.18$ for JADAS10, $P = 0.14$ for cJADAS10). The proportion of parents not satisfied with illness outcome and the proportions of patients with morning stiffness and with newly prescribed medications at the time of the visit increased progressively from ID through HDA (Figure 2).

In the same data sets, using 2012–2014 cutoffs for oligoarthritis, the level of pain and functional ability and the count of joints with restricted function were not significantly different between patients with MiDA and patients with MoDA, for both the JADAS10 and the cJADAS10 (Figure 1 in the Supplementary Appendix, on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41879/abstract). Using the 2021 cutoffs, all comparisons in post hoc analyses of polyarthritis were significant.

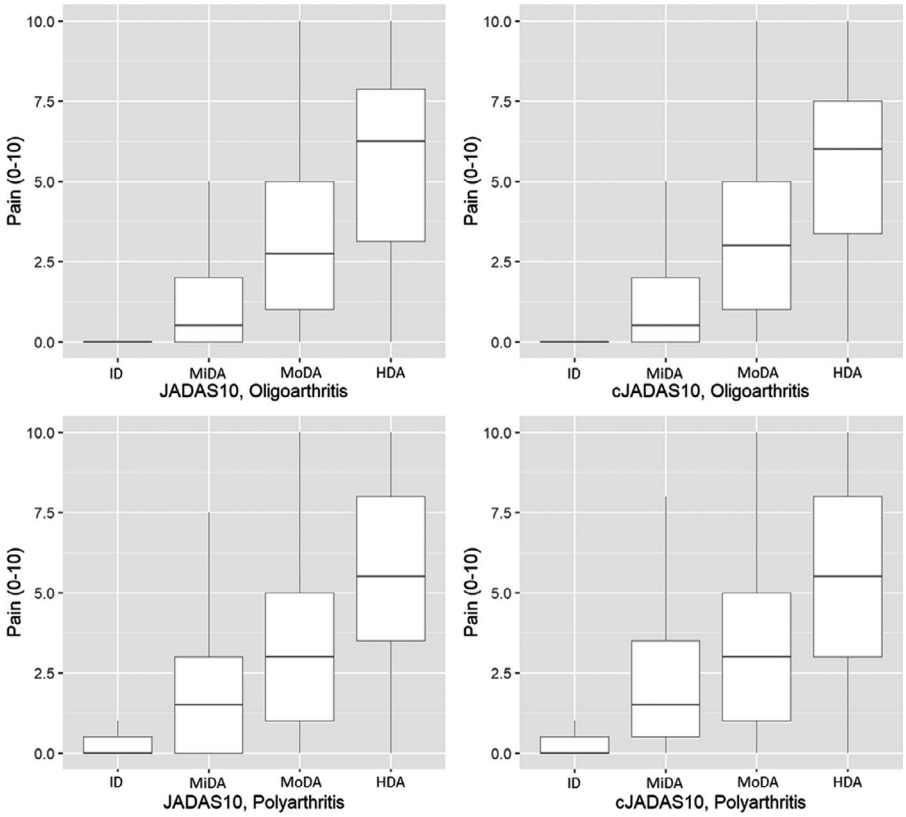

Figure 1. Comparison of the level of pain, measured on a 21-point 0–10 Likert scale, at visits (n = 1,908 for oligoarthritis and 2,489 for polyarthritis) in the Epidemiology, Treatment and Outcome of Childhood Arthritis study among patients with Juvenile Arthritis Disease Activity Score 10 (JADAS10)– and clinical JADAS10 (cJADAS10)–based inactive disease (ID), those with minimal disease activity (MiDA), those with moderate disease activity (MoDA), and those with high disease activity (HDA). Data are presented as box plots, where the boxes represent the 25th to 75th percentiles, the lines within the boxes represent the median, and the lines outside the boxes represent the range. $P < 0.001$ for comparison of disease states.

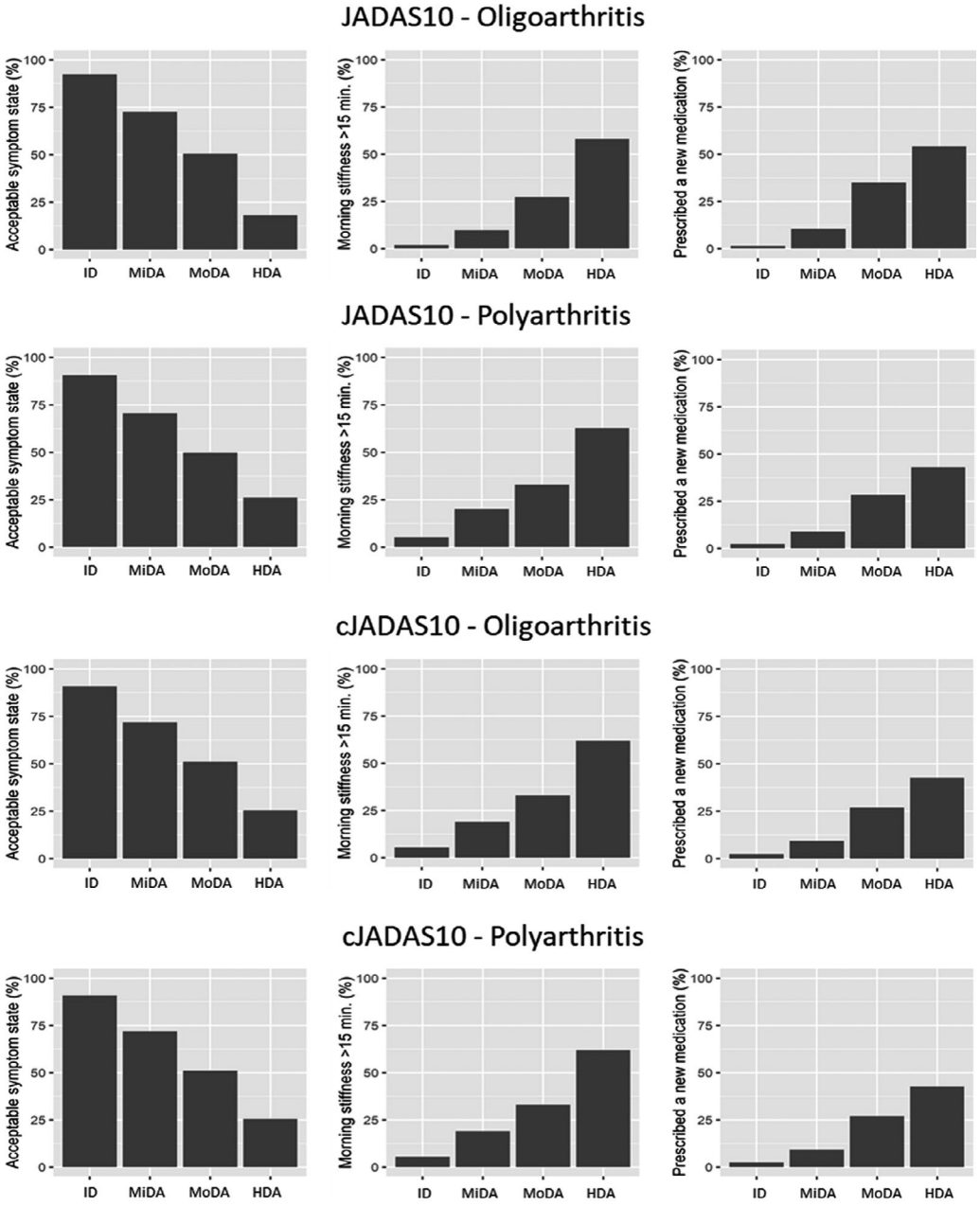

Figure 2. Percentage of patients whose parents described the patient's symptom status as acceptable, who had morning stiffness of >15 minutes, and who were prescribed a new medication for juvenile idiopathic arthritis at visits (n = 1,908 for oligoarthritis and 2,489 for polyarthritis) in the Epidemiology, Treatment and Outcome of Childhood Arthritis study among patients with Juvenile Arthritis Disease Activity Score 10 (JADAS10)– and clinical JADAS10 (cJADAS10)–based inactive disease (ID), those with minimal disease activity (MiDA), those with moderate disease activity (MoDA), and those with high disease activity (HDA). In post hoc analyses with Bonferroni correction, all comparisons were significant at $P < 0.001$ with the following exceptions: $P = 0.04$ for the comparison of morning stiffness frequency in oligoarthritis patients between the cJADAS10 states of MiDA and MoDA, and $P = 0.37$ for the comparison of the frequency of new therapy prescription in oligoarthritis patients between the cJADAS10 states of MiDA and MoDA.

In oligoarthritis and polyarthritis, the frequency of new medication prescription was not different between patients with ID and patients with MiDA according to 2012–2014 cutoffs for JADAS10 and cJADAS10. Additionally, in oligoarthritis, the frequency of morning stiffness was not different between patients with MiDA and patients with MoDA according to 2012–2014 cutoffs for JADAS10 and cJADAS10 (Figure 2 in the Supplementary Appendix).

Ability to discriminate among different levels of improvement. The analysis included 148 oligoarthritis patients enrolled in the TRIMECA trial and 99 polyarthritis patients included in the abatacept trial. In the TRIMECA trial, all patients who exhibited an ACR Pedi 30 response at 3 months met the JADAS10 cutoffs for MoDA, whereas none met the cutoffs for ID and MiDA; of the 51 patients who exhibited an ACR Pedi 100 response,

Table 3. JIA patients with JADAS10 and cJADAS10 below the cutoff for inactive disease, with JADAS10 and cJADAS10 below the cutoff for minimal disease activity, and with JADAS10 and cJADAS10 above the cutoff for high disease activity in at least 2 visits in the first year of PharmaChild registry participation, among those with and those without clinically inactive disease according to ACR criteria at 2 years*

Visits in the first year†	Active disease at 2 years (n = 44)	Clinically inactive disease at 2 years (n = 44)	*P*
≥2 with ID by JADAS10	12 (27.3)	37 (84.1)	<0.001
≥2 with ID by cJADAS10	13 (29.5)	38 (86.4)	<0.001
≥2 with MiDA by JADAS10‡	27 (61.4)	42 (95.5)	<0.001
≥2 with MiDA by cJADAS10‡	26 (59.1)	42 (95.5)	<0.001
≥2 with HDA by JADAS10	7 (15.9)	1 (2.3)	0.064
≥2 with HDA by cJADAS10	8 (18.2)	0 (0.0)	0.009

* Values are the number (%). JIA = juvenile idiopathic arthritis; JADAS10 = Juvenile Arthritis Disease Activity Score 10; cJADAS10 = clinical JADAS10; ACR = American College of Rheumatology; ID = inactive disease; MiDA = minimal disease activity; HDA = high disease activity.
† Only patients with at least 4 visits in the first year of PharmaChild registry participation were included.
‡ Including patients with ID.

65%, 98%, and 100% met the JADAS10 cutoffs for ID, MiDA, and MoDA, respectively (Supplementary Figure 1A, http://onlinelibrary.wiley.com/doi/10.1002/art.41879/abstract). Similar data were obtained with the cJADAS10 (Supplementary Figure 1B). Of note, 1 patient in whom ID was achieved according to the JADAS10 and cJADAS10 was considered a nonresponder according to the ACR Pedi definition, due to an increase in the number of joints with limitation and a worsening in the level of physical function. The percentages of patients with JADAS10 and cJADAS10 above the cutoffs for HDA at trial baseline were 49% and 51%, respectively.

In the abatacept trial, 0%, 6%, and 56% of the patients with an ACR Pedi 30 response at 4 months met the JADAS10 cutoffs for ID, MiDA, and MoDA, respectively (Supplementary Figure 1C, http://onlinelibrary.wiley.com/doi/10.1002/art.41879/abstract); of those who exhibited an ACR Pedi 70 response, 31%, 75%, and 100% met the JADAS10 cutoffs for ID, MiDA, and MoDA, respectively. Findings with the cJADAS10 were similar (Supplementary Figure 1D). The percentages of patients with JADAS10 and cJADAS10 scores above the cutoffs for HDA at trial baseline were 63% and 68%, respectively.

According to 2012–2014 cutoffs, at least 50% of the patients with an ACR Pedi 30 to ACR Pedi 90 response in the TRIMECA trial would be classified as having HDA. In the abatacept trial, the percentage of patients with MiDA among patients who were ACR Pedi 70 responders according to 2012–2014 cutoffs did not exceed 40% (Figure 3 in the Supplementary Appendix, http://onlinelibrary.wiley.com/doi/10.1002/art.41879/abstract).

Ability to predict future disease outcome. The PharmaChild longitudinal sample included 88 patients, 33 of whom had persistent oligoarthritis. Among the patients with CID (n = 44) and those without CID (n = 44) by ACR JIA criteria at 2 years, the median number of visits with a JADAS10 score below the cutoff for ID, a JADAS10 score below the cutoff for MiDA, and a JADAS10 score above the cutoff for HDA, respectively, in the first year was 4 (IQR 2–5), 5 (IQR 4–5), and 0 (IQR 0–0) in those whose disease was clinically inactive at 2 years, and 1 (IQR 0–2), 3 (IQR 1–4), and 0 (IQR 0–1) in those whose disease was not clinically inactive at 2 years ($P < 0.001$, $P < 0.001$, and $P = 0.031$, respectively). Similar results were obtained with the cJADAS10 (data not shown). Among the patients with CID according to the ACR criteria at 2 years, the percentage of visits in the first year in which the patient had ID or MiDA was higher, and the percentage in which the patient had HDA was lower, compared to the percentages among patients whose disease was active at 2 years (Table 3). Results from the same analysis performed using 2012–2014 cutoffs are shown in Table 1 in the Supplementary Appendix.

DISCUSSION

In this study, we defined cutoffs in the JADAS10 and cJADAS10 that correspond to the states of ID, MiDA, MoDA, and HDA in juvenile oligoarthritis and RF-negative polyarthritis, based on the subjective perception of disease activity level by pediatric rheumatologists from different regions of the world. We propose that the new cutoffs be called the 2021 JADAS10 and cJADAS10 cutoffs, to distinguish them from the previous cutoffs developed in 2012 and 2014 (11–13). Cutoff development was conducted using a large multinational data set comprising nearly 2,000 patients enrolled in 35 pediatric rheumatology centers located in 49 countries on 5 continents. The large sample size and the wide geographic distribution of the centers make the study findings likely generalizable to patients with various JIA phenotypes and treated with different approaches. Notably, the new cutoffs are closer to the JADAS thresholds identified by Swart et al for treatment escalation from a cohort of JIA patients seen at an academic center (28).

We considered it necessary to develop new cutoff values because previous JADAS and cJADAS cutoffs were developed

using formal criteria for CID (14) and MiDA (15) as reference standards, but both of these definitions comprise some JADAS components, making it difficult to avoid circular reasoning. Indeed, the definition of CID includes the count of joints with active arthritis, the physician global assessment of disease activity, and measurement of an acute-phase reactant. The definition of MiDA is centered on the count of joints with active arthritis, the physician global assessment of disease activity, and the parent/patient assessment of well-being. Another limitation of 2012–2014 cutoffs was the use of the physician's treatment decisions, collected retrospectively, as an external criterion. This approach did not take into account the fact that treatment changes could be driven by factors other than disease activity, such as drug intolerance or increased body weight. Furthermore, therapeutic choices may vary between physicians from different regions and according to their particular expertise and local availabilities of treatments.

For definition of the cutoffs, we adapted the methodology used by Aletaha et al (10) for the establishment of the CDAI and SDAI cutoffs. However, unlike that study, in which physicians rated multiple hypothetical patient profiles, we performed a more direct assessment by capturing disease activity ratings using actual patients. Because the proposed 2021 cutoffs are derived from real-life perception of patient disease activity by treating physicians, they may have greater face validity and practical relevance than the 2012–2014 cutoffs. The cutoff values were obtained by applying 4 different methods; of note, the tentative cutoffs yielded by agreement analysis were consistently higher than those yielded by different approaches, with the exception of the cutoff separating ID from MiDA. While the new cutoffs for distinguishing between ID and MiDA are very close to previous ones for oligoarthritis, they appear to be less stringent for polyarthritis. All cutoffs for the other disease activity states are notably higher in the new set.

The new cutoffs were validated using 4 different samples, including nearly 5,000 JIA patients. In cross-validation analyses, cutoff values differentiated well between levels of disease severity, as measured in terms of pain and count of joints with restricted function, and between patients who had or did not have morning stiffness or whose parents were satisfied or not satisfied with the outcome of the illness. In addition, the cutoffs revealed a strong ability to discriminate between different levels of ACR Pedi response in 2 randomized clinical trials. Notably, the cutoff values separating ID from MiDA in polyarthritis were met in a sizable proportion of cases only among patients with at least an ACR Pedi 70 response, which is in accordance with our previous findings that only an improvement in symptoms of at least 70% makes a substantial difference in disease status in patients with JIA (5). Nearly all ACR Pedi 100 responders with polyarthritis and the large majority with oligoarthritis met the cutoffs for ID. Finally, in the PharmaChild registry, achievement of the new cutoffs in the first year of observation was found to predict the attainment of disease remission at 2 years.

Our results should be interpreted in light of some potential caveats. The assessors were not provided any background information on the definition of the various disease states that could help to enhance standardization of assessments. Furthermore, although the wide geographic representation of the pediatric rheumatologists who provided their ratings is a strength of our study, it could be argued that perception of disease activity may vary between physicians practicing in different regions or with diverse expertise and treatment availability. However, the fact that the reported cutoffs were based on the judgment of physicians from a large number of countries may lead to their widespread acceptance and use and foster the harmonization of clinical assessment in JIA. In addition, we decided to limit our study only to oligoarthritis and RF-negative polyarthritis owing to the wide clinical homogeneity between these 2 JIA categories. The application of the new cutoffs in different JIA categories, and in particular to RF-positive patients, who are included in most clinical trials on polyarthritis, requires validation. Recently, a systemic JIA–specific version of the JADAS was developed and validated (29), and cutoffs specific to this tool are needed. Finally, it must be acknowledged that part of the validation analysis (predictive ability assessment and ability to discriminate among different levels of improvement) was performed in a smaller subset of patients.

The comparison of the newer versus the older sets of criteria showed a better discriminative ability with the 2021 cutoffs, particularly for oligoarthritis. Moreover, the disease activity states based on the new cutoffs appear more consistent with the response to treatment defined with the ACR Pedi criteria in 2 clinical trials. In the comparison of predictive ability, the performances of cutoffs for inactive disease were similar. Compared to use of the 2012–2014 cutoffs, the percentage of patients with active disease at 2 years was relevantly higher among those who had at least 2 visits with a JADAS score below the cutoff for MiDA in the first year according to the 2021 cutoffs. Among patients with HDA at ≥2 visits in the first year according to 2021 cutoffs, a lower proportion had clinically inactive disease at 2 years.

In conclusion, we have developed a new set of JADAS10 and cJADAS10 cutoffs for the different disease activity states in JIA, which were based on the subjective perception of the level of disease activity by a multinational sample of pediatric rheumatologists. In validation analyses, the cutoffs demonstrated a strong ability to discriminate between different levels of disease severity and treatment response and to predict the achievement of long-term disease remission. Future studies should assess the 2021 cutoffs in other prospective patient cohorts and compare their metrologic performances to those of the 2012–2014 cutoffs.

ACKNOWLEDGMENTS

We are grateful to all of the Paediatric Rheumatology International Trials Organisation EPOCA Study Group researchers and to Dr. Alyssa Dominique (Bristol Myers Squibb), for providing access to the data from the abatacept trial. We also thank Drs. Ngoc-Phoi Duong, Brigitte Bader-Meunier, Richard Mouy, Florence Aeschlimann, Chantal Job-Deslandre, Isabelle Melki, and Caroline Freychet and Thl Thanh Thao Truong and Ngoc-Bao Duong (Hôpital Necker-Enfants Malades) for data collection in France.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Consolaro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ruperto, Ravelli, Consolaro.

Acquisition of data. Nikishina, Lahdenne, Rutkowska-Sak, Avcin, Quartier, Panaviene, Uziel, Pruunsild, Vargova, Vilaiyuk, Dolezalova, Ringold, Garrone.

Analysis and interpretation of data. Trincianti, Van Dijkhuizen, Alongi, Mazzoni, Swart.

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Arthritis Care & Research
Vol. 71, No. 6, June 2019, pp 717–734
DOI 10.1002/acr.23870
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SPECIAL ARTICLE

2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the health care provider in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes, but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision, as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

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Objective. To develop treatment recommendations for children with juvenile idiopathic arthritis manifesting as non-systemic polyarthritis, sacroiliitis, or enthesitis.

Methods. The Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions were developed and refined by members of the guideline development teams. A systematic review was conducted to compile evidence for the benefits and harms associated with treatments for these conditions. GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was used to rate the quality of evidence. A group consensus process was conducted among the Voting Panel to generate the final recommendations and grade their strength. A Parent and Patient Panel used a similar consensus approach to provide patient/caregiver preferences for key questions.

Results. Thirty-nine recommendations were developed (8 strong and 31 conditional). The quality of supporting evidence was very low or low for 90% of the recommendations. Recommendations are provided for the use of nonsteroidal antiinflammatory drugs, disease-modifying antirheumatic drugs, biologics, and intraarticular and oral glucocorticoids. Recommendations for the use of physical and occupational therapy are also provided. Specific

This article is published simultaneously in *Arthritis & Rheumatology*.

Supported by the American College of Rheumatology and the Arthritis Foundation. Dr. Angeles-Han's work was supported by the NIH (grant K23-EY-021760 from the National Eye Institute), the Rheumatology Research Foundation, and the Cincinnati Children's Hospital Medical Center Research Innovation and Pilot fund. Drs. Colbert and Ombrello's work was supported by the NIH (grants AR-041184 and AR-041198, respectively, from the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases). Dr. Ferguson's work was supported by the NIH (grant AR-059-703). Dr. Nigrovic's work was supported by the Fundación Bechara.

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recommendations for polyarthritis address general medication use, initial and subsequent treatment, and adjunctive therapies. Good disease control, with therapeutic escalation to achieve low disease activity, was recommended. The sacroiliitis and enthesitis recommendations primarily address initial therapy and adjunctive therapies.

Conclusion. This guideline provides direction for clinicians, caregivers, and patients making treatment decisions. Clinicians, caregivers, and patients should use a shared decision-making process that accounts for patients' values, preferences, and comorbidities. These recommendations should not be used to limit or deny access to therapies.

INTRODUCTION

Juvenile arthritis is one of the most common chronic diseases of childhood, with an estimated prevalence of 1 per 1,000 children (1–3). The term juvenile idiopathic arthritis (JIA) defines a heterogeneous collection of inflammatory arthritides of unknown etiology with onset prior to age 16 years and a minimum duration of 6 weeks, following the exclusion of other known causes of synovitis (4). Current International League of Associations for Rheumatology (ILAR) classification criteria divide JIA into 7 mutually exclusive categories defined by the number of joints involved, presence or absence of extraarticular manifestations, and presence or absence of additional markers including rheumatoid factor (RF) and HLA–B27 (4).

All forms of JIA are associated with decreased health-related quality of life and risk of permanent joint damage, and the disease may persist into adulthood, causing ongoing significant morbidity and impaired quality of life (5–13). A number of treatments are available, including nonsteroidal antiinflammatory drugs (NSAIDs), systemic and intraarticular glucocorticoids, and nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs). Prompt initiation of appropriate therapy is of critical importance in preventing permanent damage and improving outcomes. While earlier disease recognition and expanded treatment options have made good disease control a possibility for many patients, they have also made the decision-making regarding treatments more complex for physicians, caregivers, and patients.

The American College of Rheumatology (ACR) published initial recommendations for JIA in 2011 that provided guidance for the treatment of JIA and for the monitoring of select medical therapies, and an update in 2013 focused on the treatment of systemic arthritis (14,15). The ACR has subsequently transitioned from the RAND/UCLA Appropriateness Method used to generate these prior recommendations to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, which has the advantages of a more transparent decision-making process and well-defined criteria for moving from evidence to recommendation, including balancing benefits and harms and consideration of patient values and preferences while maintaining methodologic rigor (16).

The goal of this guideline project was to provide updated recommendations for juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis, incorporating recently published data and utilizing the GRADE methodology. Recommendations for the treatment of chronic and acute JIA-associated uveitis were developed concomitantly and are presented separately (17).

METHODS

Methodology overview. This guideline followed the ACR guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process includes using the GRADE methodology (www.gradeworkinggroup.org) to rate the quality of the available evidence and to develop the recommendations (18–20). ACR policy guided disclosures and the management of conflicts of interest (participant disclosures are available at https://www.rheumatology.org/Portals/0/Files/JIA-Guideline-Disclosures.pdf). Supplementary Appendix 1, available on the *Arthritis Care & Research* web site

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Dr. Beukelman has received consulting fees from Bristol-Myers Squibb, Sobi, UCB, and Novartis (less than $10,000 each). Dr. Lovell has received consulting fees from AstraZeneca, Amgen, Abbott, Wyeth Pharmaceuticals, Pfizer, Hoffmann-La Roche, Novartis, UCB, Takeda, Janssen, GlaxoSmithKline, Boehringer Ingelheim, Celgene, Bristol-Myers Squibb, and AbbVie (less than $10,000 each). Dr. Nigrovic has received consulting fees from Bristol-Myers Squibb, Pfizer, AbbVie, Novartis, and Sobi (less than $10,000 each) and research grants from Sobi, Novartis, AbbVie, and Genentech (in support of the FROST study of systemic JIA through CARRA). Dr. Stoll has received speaking fees from Novartis (less than $10,000). Dr. Rabinovich has received consulting fees from AbbVie (less than $10,000). Dr. Schneider has received consulting fees from Novartis and Sobi (less than $10,000 each). No other disclosures relevant to this article were reported.

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Submitted for publication August 31, 2018; accepted in revised form February 27, 2019.

at http://onlinelibrary.wiley.com/doi/10.1002/acr.23870/abstract, describes the methods in detail.

Guideline development teams. This work involved 5 teams: 1) a Core Leadership Team, consisting of 4 pediatric rheumatologists, who supervised and coordinated the project and assisted with developing the scope of the project and initial Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions and drafting the manuscript; 2) a Literature Review Team, led by an experienced literature review consultant, which completed the literature search and data abstraction and rated the quality of evidence; 3) an Expert Panel, composed of 9 pediatric rheumatologists, who assisted with developing the scope of the project and drafting and refining the PICO questions; 4) a Voting Panel, consisting of 15 pediatric rheumatologists and 2 adult patients with JIA, who assisted with developing the scope of the project and refining the PICO questions and voted on the recommendations; and 5) a Parent and Patient Panel, consisting of 9 adult patients with JIA and 2 parents of children with JIA, who reviewed the collated evidence and provided input on their values and preferences within the context of a separate meeting. Supplementary Appendix 2 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23870/abstract) presents rosters of the team and panel members. In accordance with ACR policy, the principal investigators and the literature review consultant were free of potential conflicts of interest, and in all teams, >50% of members were free of potential conflicts of interest.

PICO question development and importance of outcomes. The Core Leadership Team drafted the initial project scope, key principles, and examples of relevant PICO questions. The following topics were proposed to the guideline development groups for consideration: acute and chronic anterior uveitis, oligoarthritis, polyarthritis, systemic arthritis, sacroiliitis, enthesitis, and temporomandibular joint arthritis. PICO questions for each topic were developed and discussed at a face-to-face meeting during which the topics were refined. The project scope was subsequently limited to patients with non-systemic polyarthritis, sacroiliitis, and enthesitis, because these were deemed to be the most high-impact areas. The PICO questions for these topics were subsequently reviewed and further refined by the Expert and Voting Panels via e-mail.

Populations (Table 1). While the current ILAR classification criteria have been useful for identifying homogeneous groups of patients for research, more recent data suggest that these categories may not entirely reflect the underlying genetic and clinical heterogeneity of the disease or be relevant for guiding treatment decisions (20–22). For this reason, it was decided to base the current guideline on broad clinical phenotypes rather than ILAR categories, similar to the approach used for development of the 2011 guideline (15). The patient populations addressed in this guideline are defined below. The current recommendations are intended to address typical

Table 1. Terms and definitions*

Term	Definition
Polyarthritis population	Children with JIA and non-systemic polyarthritis (≥5 joints ever involved); may include children from ILAR JIA categories of polyarticular (rheumatoid factor positive or negative), extended oligoarticular, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis.
Risk factors	One or more of the following: positive rheumatoid factor, positive anti–cyclic citrullinated peptide antibodies, joint damage.
Moderate/high disease activity	Clinical Juvenile Disease Activity Score based on the cJADAS-10 >2.5.
Low disease activity	Clinical JADAS-10 ≤2.5 and ≥1 active joint.
Sacroiliitis population	Patients with active sacroiliitis who will most likely be classified within the ILAR categories of enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis, but may include patients in any of the ILAR JIA categories.
Active sacroiliitis	Prior or current magnetic resonance imaging findings consistent with sacroiliitis along with clinical examination findings consistent with sacroiliitis (e.g., pain with direct palpation of the sacroiliac joints) and/or patient-reported symptoms of inflammatory back pain.
Enthesitis population	Patients with enthesitis (inflammation at tendon-to-bone insertion sites) who will most likely be from the ILAR categories of enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis, but may include patients from any of the ILAR JIA categories.
Active enthesitis	Tenderness and/or swelling of the entheses determined to require medical treatment per the treatment provider.

* Disease activity (moderate/high and low) as defined by the clinical Juvenile Disease Activity Score based on 10 joints (cJADAS-10) is provided as a general parameter and should be interpreted within the clinical context. JIA = juvenile idiopathic arthritis. ILAR = International League of Associations for Rheumatology.

patients with the phenotype and may not be applicable to patients with uncommon features or highly refractory disease.

Polyarthritis. This group includes children with JIA and polyarthritis (≥5 joints ever involved) and may include children from different ILAR JIA categories but excludes children with systemic arthritis or sacroiliitis. These guidelines are not intended to be applicable to children with associated extraarticular manifestations (e.g., psoriasis, uveitis, inflammatory bowel disease) that may also influence treatment decisions. Given the heterogeneity of patients with JIA and polyarthritis, the Expert and Voting Panels initially categorized patients into treatment groups, using combinations of the following categories: 1) presence or absence of risk factors for disease severity and potentially a more refractory disease course, and 2) low disease activity versus moderate/high disease activity.

Risk factors were defined as the presence of one or more of the following: positive anti–cyclic citrullinated peptide antibodies, or joint damage. The Juvenile Arthritis Disease Activity Score (JADAS) was proposed as a means of categorizing disease activity, with the acknowledgment that a number of versions exist, and that validation is not fully complete and cutoff scores may change (23–27). A joint with inactive disease was defined using the ACR definition: presence of swelling (not due to currently inactive synovitis or to bony enlargement) or, if swelling is not present, limitation of motion accompanied by pain, tenderness, or both (28,29). The Voting Panel used the clinical JADAS based on 10 joints (cJADAS-10) and a cutoff of ≤2.5 versus >2.5 to define low versus high/moderate disease activity. Low disease activity was further defined as a cJADAS-10 of ≤2.5 and ≥1 joint with active disease to ensure that active arthritis was also present. Moderate and high disease activity were considered together, because it was thought that treatment approaches would be similar (30). The cJADAS-10 is a sum of the total active joint count (to a maximum of 10), physician's global assessment of disease activity (0–10 scale), and parent/patient's global assessment of well-being (0–10 scale). It was also acknowledged that one of the limitations of the JADAS is the lack of standardization of the physician's and parent's global assessments. It is therefore recommended that the JADAS be interpreted within the context of the clinical presentation rather than considered an absolute determinant of disease activity.

Because ultimately few data were available to support different treatment approaches based on the risk factors and disease activity categories, patients were often grouped together to provide a recommendation. The few instances in which the Voting Panel made differing recommendations based on disease activity or risk factors are explicitly noted.

Sacroiliitis. This group includes patients with active sacroiliitis who will most likely be classified within the ILAR categories of enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis but may include patients in any of the ILAR JIA categories. In addition to active sacroiliitis, patients may or may not have active peripheral joint disease and/or enthesitis to be included in this population. It is anticipated that patients with peripheral spondyloarthritis and no sacroiliitis would be treated according to the polyarthritis recommendations included in this update or existing JIA oligoarthritis treatment recommendations from the 2011 ACR JIA guideline (15), depending on the numbers of joints involved. For the purposes of this guideline, patients were considered to have active sacroiliitis if they had prior or current magnetic resonance imaging findings consistent with sacroiliitis along with clinical examination findings consistent with sacroiliitis (e.g., pain with direct palpation of the sacroiliac joints) and/or patient-reported symptoms of inflammatory back pain.

Enthesitis. This group is intended to include patients with enthesitis (inflammation at tendon-to-bone insertion sites) who will also most likely be from the ILAR categories of enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis but may include patients from any of the ILAR JIA categories. Patients may or may not have concomitant active peripheral arthritis or sacroiliitis to be included in this guideline, but the recommendations for enthesitis are intended to apply to patients with isolated enthesitis or with active enthesitis despite adequate control of their other disease manifestations. For the purposes of this guideline, active enthesitis is tenderness and/or swelling of the entheses determined to require medical treatment per the treating provider.

Interventions. The pharmacologic and nonpharmacologic therapies considered are listed in Table 2. Both intraarticular and oral glucocorticoids were considered. For the purposes of the recommendations, a bridging course of oral glucocorticoids was defined as a short course (<3 months) of oral glucocorticoids intended to control disease activity quickly during escalation of DMARD or biologic therapy, using the shortest possible duration and the lowest dose needed to control symptoms. The duration of bridging therapy would likely be primarily determined by the anticipated timing of onset of action of the other DMARD or biologic treatment(s). An optimal trial of methotrexate was considered to be 3 months; however, if no or minimal response was observed after 6–8 weeks, it was agreed that changing or adding therapy may be appropriate.

Outcomes. Outcomes were selected during the initial face-to-face scoping meeting and subsequently refined by online vote (Supplementary Appendix 3**,** available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23870/abstract). Critical outcomes included disease activity, quality of life, joint damage, and serious adverse events. Pain was selected as an important outcome. While each of these outcomes was thought to be important in decision-making by the guideline development teams, they were not routinely reported across stud-

Table 2. Interventions included in the literature review*

Intervention	Name/type
NSAIDs	Any
DMARDs	Leflunomide, methotrexate, sulfasalazine, triple non–biologic DMARD (methotrexate, sulfasalazine, hydroxychloroquine)
Biologics	
TNFi	Adalimumab, etanercept, infliximab, golimumab†
Non-TNFi‡	Abatacept (CTLA-4Ig), tocilizumab (anti–interleukin-6 receptor), rituximab (anti-CD20)
Glucocorticoids	
Oral	Any
Intraarticular	Triamcinolone acetonide, triamcinolone hexacetonide, methylprednisolone acetate
Other interventions	Physical therapy
	Occupational therapy

* NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease-modifying antirheumatic drugs; TNFi = tumor necrosis factor inhibitor.
† Certolizumab was not included in the recommendations because no pediatric data were yet available.
‡ Evaluated for polyarthritis only.

ies. Disease activity and serious adverse events were the most consistently reported outcomes.

Literature searches, data abstraction, and rating the quality of evidence. Systematic searches of the published English-language literature included Ovid Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from the beginning of each database through June 12, 2017 (see Supplementary Appendix 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23870/abstract); updated searches were conducted on October 13, 2017. DistillerSR software (https://distillercer.com/products/distillersr-systematic-reviewsoftware/) facilitated duplicate screening of literature search results. Supplementary Appendix 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23870/abstract, shows the citation flow chart. Reviewers entered extracted data into RevMan software (http://tech.cochrane.org/revman) and evaluated the risk of bias of primary studies using the Cochrane risk of bias tool (http://handbook.cochrane.org/). RevMan files were exported into GRADEpro software to formulate a table showing the GRADE summary of findings (Supplementary Appendix 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23870/abstract) for each PICO question (31).

When available, the evidence summaries included the benefits and harms for outcomes of interest across studies, the relative effect (95% confidence interval), the number of participants, and the absolute effects. GRADE criteria provided the framework for judging the overall quality of evidence (16). The Literature Review Team rated the quality of evidence for each critical and important outcome as high, moderate, low, or very low quality, taking into account limitations of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. The overall quality listed in this report for a body of evidence (i.e., either an individual article or a group of articles) is not a statement about the methodologic quality of the study (or studies). Rather, the intention was to rate the article(s) in relation to the PICO question under consideration. As a result, a very well-conducted study might be rated lower in the evidence report. For example, if the population or intervention being studied does not completely match the population or intervention being examined by the PICO question, the evidence is downgraded for indirectness. The overall quality of evidence may also be downgraded due to imprecision in the effect estimate (e.g., wide confidence intervals or a low number of patients or events).

During the Voting Panel meeting, the panel also considered relevant data from adult studies, but these studies were not systematically searched or compiled in the evidence report. The Voting Panel was provided with a copy of the evidence report from the ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis as a reference (32) (https://www.rheumatology.org/Portals/0/Files/Axial-SpA-Guideline-Supplement-E.pdf).

Moving from evidence to recommendations. Each recommendation was made based on a consideration of the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (e.g., confidence in the effect estimates), and patients' values and preferences, as per GRADE methodology. Discussion points and voting results from the Parent and Patient Panel meeting were presented during the Voting Panel meeting, as relevant. When the literature did not clearly guide recommendations, recommendations were based on the experience of the Voting Panel members (including physicians and the 2 patients present) as well as the results from the Parent and Patient Panel. Financial costs were not formally considered during the voting process.

Consensus building. The Voting Panel voted on the direction and strength of the recommendation related to each PICO question. Recommendations required a 70% level of

agreement; if 70% agreement was not achieved during an initial vote, the panel members held additional discussions before re-voting, including rewording of recommendations if needed, until consensus was attained (33). Discussion and iterative voting occurred until consensus was achieved. An additional round of voting was conducted online after the Voting Panel meeting to address questions that arose during preparation of the final recommendations. For each recommendation, a written explanation is provided, describing the reasons for this decision and conditions under which the alternative choice may be preferable, when relevant.

Moving from recommendations to practice. These recommendations are designed to help health care providers, caregivers, and patients engage in shared decision-making regarding treatment choices. Health care providers, caregivers, and patients must take into consideration not only clinical phenotype and level of disease activity but also comorbidities, response to and tolerance of prior therapies, patient's values and preferences, and patient's functional status and functional goals when choosing the optimal therapy for an individual patient at the given point in treatment.

RESULTS/RECOMMENDATIONS

How to interpret the recommendations (18–20)

1. A *strong* recommendation means that the Voting Panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion would not want to follow the recommendation. In some cases, strong recommendations were made even in the absence of moderate- or high-quality evidence based on Voting Panel experience and data from adult studies.
2. A *conditional* recommendation means that the Voting Panel believed that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are particularly preference-sensitive and warrant a shared decision-making approach. Conditional recommendations were generally based on low- to very low–quality evidence. Most recommendations in this guideline are conditional.
3. For each recommendation, Supplementary Appendix 6 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23870/abstract) provides details regarding the PICO questions and the GRADE evidence tables. PICO questions were combined when possible to create simplified recommendations.

General recommendations for patients with JIA and polyarthritis (Table 3)

For this population, an initial set of general recommendations was made regarding NSAID, DMARD, intraarticular glucocorticoid, and biologic use. These general recommendations are intended to apply to the subsequent specific polyarthritis recommendations addressing these medications, because the recommendations were not anticipated to differ based on initial versus subsequent therapy, level of disease activity, or presence or absence of risk factors. For example, in PICO A.2 and A.3, methotrexate is conditionally recommended over leflunomide and sulfasalazine. It is intended that this recommendation apply to subsequent recommendations referring to DMARD therapy.

Each recommendation in this section is prefaced with the statement "In children and adolescents with JIA and active polyarthritis…"

PICO A.1. *NSAIDs are conditionally recommended as adjunct therapy*. This recommendation is conditional based on the very low quality of evidence and incorporation of patient and caregiver preferences, particularly concerns regarding medication adverse effects. In general, NSAIDs were thought to be appropriate for symptom management, particularly during initiation or escalation of therapy with DMARDs or biologics (34–36). It was acknowledged that NSAIDs are not appropriate as monotherapy for chronic, persistent synovitis.

PICO A.2–A.3. *Using methotrexate is conditionally recommended over leflunomide or sulfasalazine*.

Leflunomide. The quality of supporting evidence for this recommendation was moderate. The recommendation to favor methotrexate over leflunomide is due to the greater volume of data supporting the effectiveness of methotrexate. The Voting Panel also specifically noted the lack of data for the dosing, safety, and effectiveness of leflunomide in children younger than age 3 years and lack of long-term safety data for leflunomide in general for children with polyarthritis (37,38). In addition, there currently is no liquid form of this medication, which may make administration difficult, particularly in younger children.

Sulfasalazine. The recommendation for methotrexate over sulfasalazine is conditional, because the supporting evidence is of very low quality, there are no head-to-head comparison studies, and there are more data supporting the effectiveness of methotrexate. There were also concerns raised by the Voting Panel regarding the safety of sulfasalazine as compared to methotrexate, specifically the risk of Stevens-Johnson syndrome and bone marrow suppression (35,36).

Although methotrexate is conditionally recommended over each of these therapies, it is important to note that the Parent and Patient Voting Panel participants stated that they would want to be made aware of available alternatives to methotrexate, because

Table 3. General medication recommendations for children and adolescents with JIA and polyarthritis*

Recommendation	Level of evidence
Each recommendation is preceded by the phrase: *"In children and adolescents with JIA and active polyarthritis…"*	
NSAIDs	
• NSAIDs are conditionally recommended as adjunct therapy (PICO A.1).	Very low
DMARDs	
• Using methotrexate is conditionally recommended over leflunomide or sulfasalazine (PICO A.2, A.3).	Moderate (leflunomide); very low (sulfasalazine)
• Using subcutaneous methotrexate is conditionally recommended over oral methotrexate (PICO A.4).	Very low
Glucocorticoids	
• Intraarticular glucocorticoids are conditionally recommended as adjunct therapy (PICO A.5).	Very low
• Triamcinolone hexacetonide is ***strongly*** recommended over triamcinolone acetonide for intraarticular glucocorticoid injections (PICO A.6).	Moderate
• Bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy in patients *with high or moderate disease activity* is conditionally recommended (PICO A.7).† Bridging therapy may be of most utility in the setting of limited mobility and/or significant symptoms.	Very low
• Conditionally recommend *against* bridging therapy with a limited course of oral glucocorticoids (<3 months) in patients with *low disease activity* (PICO A.8).	Very low
• ***Strongly*** recommend *against* adding chronic low-dose glucocorticoid, irrespective of risk factors or disease activity (PICO A.9).	Very low
Biologic DMARDs	
• In children and adolescents with JIA and polyarthritis initiating treatment with a biologic (etanercept, adalimumab, golimumab, abatacept, or tocilizumab) combination therapy with a DMARD is conditionally recommended over biologic monotherapy (PICO A.10, A.11, A.12, A.13, A.14).	Very low (etanercept, golimumab); low (abatacept, tocilizumab); moderate (adalimumab)
• Combination therapy with a DMARD is ***strongly*** recommended for infliximab (PICO A.15).	Low
Physical therapy and occupational therapy	
• In children and adolescents with JIA and polyarthritis who have or are at risk of functional limitations, using physical therapy and/or occupational therapy is conditionally recommended (PICO A.16, PICO A.17).	Low (physical therapy); very low (occupational therapy)

* JIA = juvenile idiopathic arthritis; NSAIDs = nonsteroidal antiinflammatory drugs; PICO = Patient/Population, Intervention, Comparison, and Outcomes; DMARDs = disease-modifying antirheumatic drugs.
† A bridging course of oral glucocorticoids was defined as a short course (<3 months) of oral glucocorticoids intended to control disease activity quickly during the initiation or escalation of therapy. An adequate trial of methotrexate was considered to be 3 months. If no or minimal response is observed after 6–8 weeks, it was agreed that changing or adding therapy may be appropriate.

the adverse effects of methotrexate, particularly gastrointestinal intolerance, are very limiting for some children.

PICO A.4. *Using subcutaneous methotrexate is conditionally recommended over oral methotrexate*. This recommendation is conditional, because the supporting evidence is of very low quality, and patient preferences may guide the choice of route of administration (39–46). The strength of the recommendation also reflects Voting Panel experience, lack of certainty regarding differences in adverse event rates between the 2 routes of administration, consideration of data suggesting variable bioavailability of oral methotrexate (particularly at higher doses), and the goal of optimizing methotrexate effectiveness prior to escalating therapy (47,48).

PICO A.5. *Intraarticular glucocorticoids are conditionally recommended as adjunct therapy*. This recommendation is conditional given that the supporting evidence is of very low quality and was primarily generated in children with oligoarthritis, and given the variable parent and patient experiences and preferences regarding a procedure that may require sedation or be painful (49). In addition, intraarticular glucocorticoid injections may not be an appropriate treatment approach for large numbers of joints or joints that have been injected multiple times; escalation of systemic therapy may be preferred in these situations. The Voting Panel also suggested that intraarticular glucocorticoid injections be more strongly considered when arthritis is preventing ambulation or otherwise interfering with important daily activities and more prompt disease control is needed.

Table 4. General guidelines for the initial and subsequent treatment of children and adolescents with JIA and polyarthritis*

Recommendation†	Level of evidence
Each recommendation is preceded by the phrase: ***"In children and adolescents with JIA and active polyarthritis…"***	
Initial therapy	
All patients	
• Initial therapy with a DMARD is ***strongly*** recommended over NSAID monotherapy (PICO B.1).	Moderate
• Using methotrexate monotherapy as initial therapy is conditionally recommended over triple DMARD therapy (PICO B.2).	Low
Patients without risk factors:†	
• Initial therapy with a DMARD is conditionally recommended over a biologic (PICO B.3).	Low
Patients with risk factors:	
• Initial therapy with a DMARD is conditionally recommended over a biologic, recognizing that there are situations where initial therapy that includes a biologic may be preferred (PICO B.4). Initial biologic therapy may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, or hip), high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage.	Low
Subsequent therapy: Low disease activity (cJADAS-10 ≤2.5 and ≥1 active joint) For children receiving a DMARD and/or biologic:	
• Escalating therapy is conditionally recommended over no escalation of therapy (PICO B.5, B.6). Escalation of therapy may include: Intraarticular glucocorticoid injection(s), optimization of DMARD dose, trial of methotrexate if not done, and adding or changing biologic.	Very low
Subsequent therapy: Moderate/high disease activity (cJADAS-10 >2.5) If patient is receiving DMARD monotherapy:	
• Adding a biologic to original DMARD is conditionally recommended over changing to a second DMARD (PICO B.7).	Low
• Adding a biologic is conditionally recommended over changing to triple DMARD therapy (PICO B.8).	Low
If patient is receiving first TNFi (± DMARD):	
• Switching to a non-TNFi biologic (tocilizumab or abatacept) is conditionally recommended over switching to a second TNFi (PICO B.9). A second TNFi may be appropriate for patients with good initial response to their first TNFi (i.e., secondary failure).	Very low
If patient is receiving second biologic:	
• Using TNFi, abatacept, or tocilizumab (depending on prior biologics received) is conditionally recommended over rituximab (PICO B.10).	Very low

* Disease activity (moderate/high and low) as defined by the clinical Juvenile Disease Activity Score based on 10 joints (cJADAS-10) is provided as a general parameter and should be interpreted within the clinical context. TNFi = tumor necrosis factor (etanercept, adalimumab, infliximab, golimumab) (see Table 3 for other definitions).
† Risk factors include the presence of any of the following: positive anti–cyclic citrullinated peptide antibodies, positive rheumatoid factor, or presence of joint damage. An adequate trial of methotrexate was considered to be 3 months. If no or minimal response is observed after 6–8 weeks, it was agreed that changing or adding therapy may be appropriate. For the purposes of these recommendations, triple DMARD therapy is methotrexate, sulfasalazine, and hydroxychloroquine. The term biologic refers to TNFi, abatacept, or tocilizumab for each of the recommendations, with the exception of PICO B.10, which includes rituximab. Shared decision-making between the physician, parents, and patient, including discussion of recommended treatments and potential alternatives, is recommended when initiating or escalating treatment.

PICO A.6. *Triamcinolone hexacetonide is **strongly** recommended over triamcinolone acetonide for intraarticular glucocorticoid injections*. The quality of supporting evidence for this recommendation was moderate (50). This recommendation was further supported by observational studies showing improved outcomes with triamcinolone hexacetonide in oligoarticular JIA and rheumatoid arthritis (RA) (51,52). Voting panel members specifically noted their consistent and repeated observation of more complete and longer duration of clinical response without increased adverse effects with triamcinolone hexacetonide versus triamcinolone acetonide. The Parent and Patient Voting Panel also supported this judgment on the strength of the recommendation.

PICO A.7. *Bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy in patients with high or moderate disease activity is conditionally recommended*. This recommendation is conditional based on very low quality of supporting evidence and the known risks associated with systemic glucocorticoid treatment. Parents and patients agreed that bridging therapy was acceptable in this setting. Bridging therapy with glucocorticoids may have most utility

in the setting of high disease activity, limited mobility, and/or significant symptoms.

PICO A.8. *Conditionally recommend **against** bridging therapy with a limited course of oral glucocorticoids (<3 months) in patients with low disease activity*. The quality of evidence for this recommendation was very low. Intraarticular glucocorticoid injection was considered preferable in this setting.

PICO A.9. ***Strongly** recommend **against** adding chronic low-dose glucocorticoids, irrespective of risk factors or disease activity*. The quality of supporting evidence for this recommendation was very low. The recommendation was strong, however, given the known adverse effects of long-term systemic glucocorticoid treatment in children, particularly growth suppression, weight gain, osteopenia and cataracts, and availability of other treatment options. The Voting Panel agreed that in the setting of low disease activity, targeted joint injections may be more appropriate (PICO A.5). In the setting of moderate or high disease activity, escalating DMARD or biologic therapy is likely more appropriate.

PICO A.10–A.14. *In children and adolescents with JIA and polyarthritis initiating treatment with a biologic (etanercept, adalimumab, golimumab, abatacept, or tocilizumab), combination therapy with a DMARD is conditionally recommended over biologic monotherapy*. This recommendation is intended for patients initiating biologics for additional disease control and not intended for patients who may be tapering therapy due to inactive disease, for whom tapering or removal of the DMARD while continuing biologic therapy may be an appropriate strategy. The available evidence addresses combination therapy with methotrexate, with no evidence identified for other DMARDs. There was variability in the quality of supporting evidence for the medications, ranging from very low (etanercept, golimumab) to low (abatacept or tocilizumab) and moderate (adalimumab) (39,53–67). The potential benefit of methotrexate treatment for prevention of antidrug antibodies to adalimumab was included in the discussion for concomitant DMARD use with that medication (61). The overall recommendation is conditional based on the quality of supporting evidence and variable parent and patient preferences given the burden of taking multiple medications and concerns regarding methotrexate intolerance. The Voting Panel recognized that there may be situations in which biologic monotherapy is also acceptable, particularly in the setting of adequate disease control or methotrexate intolerance.

PICO A.15. *Combination therapy with a DMARD is **strongly** recommended for infliximab*. Using infliximab in combination with a DMARD was a strong recommendation despite the low quality of evidence, primarily given more extensive experience with the need for combination therapy to reduce the risk of antidrug antibody formation (68,69).

PICO A.16, A.17. *In children and adolescents with JIA and polyarthritis who have or are at risk for functional limitations, using physical therapy (PT) and/or occupational therapy (OT) is conditionally recommended*. This recommendation is conditional based on the low quality of supporting evidence for PT, very low level of evidence for OT, and Voting Panel experience (70,71).

Recommendations for the initial and subsequent treatment of JIA and polyarthritis (Table 4 and Figure 1)

While the initial set of PICO questions for polyarthritis also included comparisons between specific biologics, these questions were discarded at the in-person Voting Panel meeting due to lack of evidence to guide decision-making in those scenarios. Although there is most experience with tumor necrosis factor inhibitors (TNFi) as the initial biologic, the class of initial biologic is not specified in the recommendations, again due to lack of comparative data, and the consideration that non-TNFi biologics may be preferred in certain scenarios based on patient-level factors (e.g., family history of demyelinating disease) and preferences. In the recommendations (see below), biologic therapy refers to TNFi, abatacept, or tocilizumab, with the exception of PICO B.9, in which rituximab is also addressed. Each recommendation in this section is prefaced with the statement "In children and adolescents with JIA and active polyarthritis…"

Initial therapy

PICO B.1 *Initial therapy with a DMARD is **strongly** recommended over NSAID monotherapy*. This recommendation is strong based on moderate quality of supporting evidence, known risk of permanent joint damage associated with ongoing, active disease, and Voting Panel experience (35,36,41).

PICO B.2. *Using methotrexate monotherapy as initial therapy is conditionally recommended over triple DMARD therapy*. The quality of evidence for this recommendation was low, based on the available trial being relatively small and not blinded (72). Parents and patients also expressed concerns about the burden of taking the 3 different medications, but they did state a preference to be informed about this treatment option.

PICO B.3. *For patients <u>without</u> risk factors, initial therapy with a DMARD is conditionally recommended over a biologic*. This recommendation is conditional based on low quality of supporting evidence and parent and patient differing preferences regarding the risks and benefits of DMARDs and biologics. While initial treatment with a biologic has been studied in TREAT-JIA (Trial of Early Aggressive Therapy in Polyarticular JIA) and ACUTE-JIA (Aggressive Combination Drug Therapy in Early Polyarticular JIA), the results were not thought to be conclusive enough to support

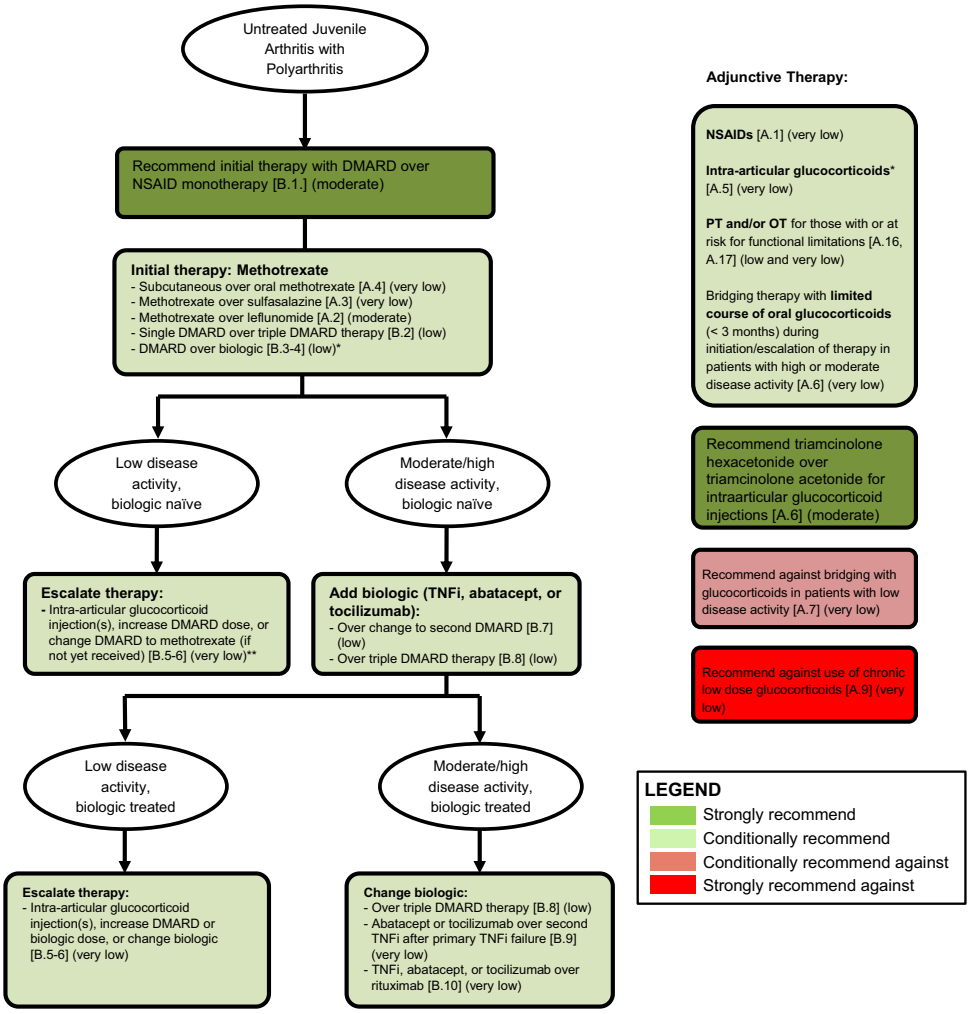
Untreated Juvenile Arthritis with Polyarthritis
Recommend initial therapy with DMARD over NSAID monotherapy [B.1.] (moderate)
Initial therapy: Methotrexate
- Subcutaneous over oral methotrexate [A.4] (very low)
- Methotrexate over sulfasalazine [A.3] (very low)
- Methotrexate over leflunomide [A.2] (moderate)
- Single DMARD over triple DMARD therapy [B.2] (low)
- DMARD over biologic [B.3-4] (low)*
Low disease activity, biologic naïve
Moderate/high disease activity, biologic naïve
Escalate therapy:
- Intra-articular glucocorticoid injection(s), increase DMARD dose, or change DMARD to methotrexate (if not yet received) [B.5-6] (very low)**
Add biologic (TNFi, abatacept, or tocilizumab):
- Over change to second DMARD [B.7] (low)
- Over triple DMARD therapy [B.8] (low)
Low disease activity, biologic treated
Moderate/high disease activity, biologic treated
Escalate therapy:
- Intra-articular glucocorticoid injection(s), increase DMARD or biologic dose, or change biologic [B.5-6] (very low)
Change biologic:
- Over triple DMARD therapy [B.8] (low)
- Abatacept or tocilizumab over second TNFi after primary TNFi failure [B.9] (very low)
- TNFi, abatacept, or tocilizumab over rituximab [B.10] (very low)
Adjunctive Therapy:
NSAIDs [A.1] (very low)
Intra-articular glucocorticoids* [A.5] (very low)
PT and/or OT for those with or at risk for functional limitations [A.16, A.17] (low and very low)
Bridging therapy with limited course of oral glucocorticoids (< 3 months) during initiation/escalation of therapy in patients with high or moderate disease activity [A.6] (very low)
Recommend triamcinolone hexacetonide over triamcinolone acetonide for intraarticular glucocorticoid injections [A.6] (moderate)
Recommend against bridging with glucocorticoids in patients with low disease activity [A.7] (very low)
Recommend against use of chronic low dose glucocorticoids [A.9] (very low)
LEGEND
Strongly recommend
Conditionally recommend
Conditionally recommend against
Strongly recommend against

Figure 1. Summary of primary recommendations for the initial and subsequent treatment of children with juvenile idiopathic arthritis (JIA) and active polyarthritis (see also Tables 3 and 4; for patients with sacroiliitis and/or enthesitis, see also Tables 5 and 6). The clinical Juvenile Arthritis Disease Activity Score based on 10 joints (cJADAS-10) was used to define low disease activity (≤2.5 with ≥1 active joint) versus moderate/high disease activity (>2.5). Although it is provided as a general parameter, the cJADAS-10 should be interpreted within the clinical context. An adequate trial of methotrexate was considered to be 3 months. If no or minimal response is observed after 6–8 weeks, it was agreed that changing or adding therapy may be appropriate. Shared decision-making between the physician, parents, and patient, including discussion of recommended treatments and potential alternatives, is recommended when initiating or escalating treatment. The Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions are shown in brackets, and quality of evidence is shown in parentheses. DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal antiinflammatory drug; PT = physical therapy; OT = occupational therapy; TNFi = tumor necrosis factor inhibitor. *DMARD therapy (methotrexate, leflunomide, or sulfasalazine) over biologic recommendation for patients without and those with risk factors, although initial biologic therapy may be appropriate for some patients with risk factors and involvement of high-risk joints, high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage. **Adding a biologic may be considered in biologic-naive patients with continued low disease activity after escalating therapy (not formally addressed in the guidelines).

biologics as initial therapy for low-risk patients (40,72). Of note, the majority of the Parent and Patient Panel voted against DMARDs as initial therapy, because a number of the participants had considerable adverse effects with methotrexate and had experienced better outcomes with biologics.

PICO B.4. *For patients with risk factors, initial therapy with a DMARD is conditionally recommended over a biologic, recognizing that there are situations where initial therapy that includes a biologic may be preferred*. This recommendation is conditional based on the low quality of supporting evidence and parent and patient differing preferences regarding the risks and benefits of DMARDs and biologics. While initial treatment with a biologic has been studied in TREAT-JIA and ACUTE-JIA, the results were not thought to be conclusive enough to support biologics as initial therapy (40,72). However, the Voting Panel acknowledged that biologics may be appropriate initial therapy for some patients *with risk factors* and involvement of high-risk joints (e.g.,

Table 5. Recommendations for the initial and subsequent treatment of children and adolescents with JIA and sacroiliitis*

Recommendation	Level of evidence
In children and adolescents with active sacroiliitis, treatment with an NSAID is ***strongly*** recommended over no treatment with an NSAID (PICO C.1).	Very low
In children and adolescents with active sacroiliitis despite treatment with NSAIDs:	
• Adding TNFi is ***strongly*** recommended over continued NSAID monotherapy (PICO C.2).	Low
• Using sulfasalazine for patients who have contraindications to TNFi or have failed more than one TNFi is conditionally recommended (PICO C.3).	Low
• ***Strongly*** recommend *against* using methotrexate monotherapy (PICO C.4).	Very low
Glucocorticoids	
In children and adolescents with active sacroiliitis despite treatment with NSAIDs:	
• Bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy is conditionally recommended (PICO C.5).† Bridging therapy may be of most utility in the setting of high disease activity, limited mobility, and/or significant symptoms.	Very low
• Intraarticular glucocorticoid injection of the sacroiliac joints as adjunct therapy is conditionally recommended (PICO C.6).	Very low
Physical therapy	
• In children and adolescents with sacroiliitis who have or are at risk for functional limitations, using physical therapy is conditionally recommended (PICO C.7).	Very low

* TNFi = tumor necrosis factor inhibitor (etanercept, adalimumab, infliximab, golimumab) (see Table 3 for other definitions).
† A bridging course of oral glucocorticoids was defined as a short course (<3 months) of oral glucocorticoids intended to control disease activity quickly during the initiation or escalation of therapy.

cervical spine, hip, and wrist), high disease activity, and/or for those judged by their physician to be at high risk of disabling joint damage. Of note, the majority of the Parent and Patient group voted against DMARDs as initial therapy, because a number of the participants had considerable adverse effects with methotrexate and had experienced better outcomes with biologics.

Subsequent therapy in patients with low disease activity (cJADAS-10 ≤2.5 and at least 1 active joint)

PICO B.5, B.6. *In patients with JIA and polyarthritis and low disease activity (cJADAS-10 ≤2.5 and at least 1 active joint) despite a DMARD or biologic, escalating therapy is conditionally recommended over no escalation of therapy*. This recommendation is conditional based on the very low quality of supporting evidence and parent and patient preferences regarding the risks and benefits of the treatment options. For this recommendation, escalating therapy is defined as any of the following: intraarticular glucocorticoid injection, increasing the DMARD or biologic dose (if not at optimal dosage), or changing biologic. Changing to an alternate DMARD (methotrexate) was suggested primarily for patients who had not yet received methotrexate and had not yet escalated to treatment with a biologic. Additional considerations included a degree of improvement while receiving current therapy

Table 6. Recommendations for the initial and subsequent treatment of children and adolescents with JIA and enthesitis*

Recommendation	Level of evidence
In children and adolescents with active enthesitis, NSAID treatment is ***strongly*** recommended over no treatment with an NSAID (PICO D.1).	Very low
In children and adolescents with active enthesitis despite treatment with NSAIDs:	
• Using a TNFi is conditionally recommended over methotrexate or sulfasalazine (PICO D.2, D.3).	Low
• Bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy is conditionally recommended (PICO D.4).† Bridging therapy may be of most utility in the setting of high disease activity, limited mobility, and/or significant symptoms.	Very low
Physical therapy	
• In children and adolescents with enthesitis who have or are at risk for functional limitations, using physical therapy is conditionally recommended (PICO D.5).	Very low

* TNFi = tumor necrosis factor inhibitor (etanercept, adalimumab, infliximab, golimumab) (see Table 3 for other definitions).
† A bridging course of oral glucocorticoids was defined a short course (<3 months) of oral glucocorticoids intended to control disease activity quickly during the initiation or escalation of therapy.

and the specific joint that was active. Synovitis preventing ambulation or otherwise interfering with important daily activities was identified as a factor that would guide more aggressive intervention (e.g., intraarticular glucocorticoid injection or adding/changing biologic).

Subsequent therapy in patients with moderate or high disease activity (cJADAS-10 >2.5)

PICO B.7. *In patients with JIA and polyarthritis and moderate or high disease activity despite DMARD monotherapy, adding a biologic to the original DMARD is conditionally recommended over changing to a second DMARD*. This recommendation was conditional based on the low quality of supporting evidence and parent and patient preferences regarding the risks and benefits of DMARDs and biologic medications (29,58,61,64,65,67,72–82).

PICO B.8. *In patients with JIA and polyarthritis and moderate or high disease activity receiving DMARD monotherapy, adding a biologic is conditionally recommended over changing to triple DMARD therapy*. The quality of evidence for this recommendation was low, based on the published pediatric trial being relatively small and not blinded (72). Although studies in RA have suggested that triple therapy is non-inferior to biologic therapy, the pediatric study showed improved outcomes for biologic therapy over triple DMARD therapy (83,84). This recommendation was also supported by Voting Panel concerns about adherence to the regimen and tolerability and parent and patient concerns about the burden of taking the 3 different medications.

PICO B.9. *In patients with JIA and polyarthritis and moderate or high disease activity receiving a first TNFi (with or without DMARD), switching to a non-TNFi biologic (tocilizumab or abatacept) is conditionally recommended over switching to a second TNFi*. This recommendation was conditional based on very low quality of supporting evidence and parent and patient preferences regarding the risks and benefits of biologics with different mechanisms of action (79,85). In making this recommendation, the Voting Panel also considered data from RA that have suggested better outcomes with switching to a non-TNFi biologic (86–88). The Voting Panel agreed that a second TNFi may be appropriate for patients who had a good initial response to their first TNFi (i.e., secondary failure), particularly failure due to the presence of suspected or measured antidrug antibodies to the first TNFi.

PICO B.10. *In patients with JIA and polyarthritis and moderate or high disease activity despite a second biologic, using a TNFi, abatacept, or tocilizumab (depending upon prior biologics received) is conditionally recommended over rituximab*. This recommendation was conditional based on very low quality of supporting evidence, Voting Panel member experience, and parent and patient preferences regarding the risks and benefits of biologics with different mechanisms of action. This recommendation was also supported by the availability of data from randomized clinical trials of tocilizumab and abatacept establishing their efficacy in JIA, which is lacking for rituximab (64,65,67). In addition, the article identified for the evidence report showed a higher rate of serious adverse events for rituximab compared to other biologics (78). The Voting Panel did discuss that rituximab may be considered earlier for RF-positive children based on data from RA, although the other 3 classes of biologics would still be primarily recommended (89).

Recommendations for the treatment of JIA and sacroiliitis (Table 5)

PICO C.1. *In children and adolescents with JIA and active sacroiliitis, treatment with an NSAID is **strongly** recommended over no treatment with an NSAID*. This recommendation was strong despite very low quality of supporting evidence in children, given the established utility of NSAIDs in adult spondyloarthritis and the analgesic effects of NSAIDs in children with other forms of arthritis. This recommendation is in alignment with the treatment recommendations for ankylosing spondylitis co-developed by the American College of Rheumatology/Spondylitis Association of America Spondyloarthritis Research and Treatment Network (32).

PICO C.2. *In children and adolescents with active sacroiliitis despite NSAIDs, adding a TNFi is **strongly** recommended over continued NSAID monotherapy*. Although the quality of supporting evidence in pediatrics for this recommendation was low, this recommendation is based on evaluation of both pediatric data and data from adult spondyloarthritis that include randomized controlled trials showing benefit (80,90–99).

PICO C.3. *In children and adolescents with active sacroiliitis despite NSAIDs, using sulfasalazine for patients who have contraindications to TNFi or have failed more than one TNFi is conditionally recommended*. This recommendation was conditional based on low quality of supporting evidence, particularly the relatively limited efficacy of sulfasalazine demonstrated in a randomized controlled trial in juvenile spondyloarthritis (100). However, it was considered as a potential option for patients with contraindications to TNFi and based on parent and patient considerations of the risks and benefits of biologics versus sulfasalazine. Sulfasalazine was also considered as an option for patients with adverse events associated with their initial TNFi that would be considered a class effect and who would therefore not be able to receive additional TNFi. Non-TNFi biologics

(e.g., interleukin-17 [IL-17] inhibitors) were not considered by the Voting Panel, because there are no published pediatric studies.

PICO C.4. *In children and adolescents with active sacroiliitis despite NSAIDs,* ***strongly*** *recommend against using methotrexate monotherapy*. Although the quality of supporting evidence for this recommendation was very low, this recommendation is based on data from adult spondyloarthritis suggesting lack of effectiveness (92,101–103). While we recommend against using methotrexate monotherapy as a treatment for sacroiliitis, methotrexate may have utility as adjunct therapy in patients with concomitant peripheral polyarthritis or to prevent the development of antidrug antibodies against monoclonal TNFi.

PICO C.5. *In children and adolescents with active sacroiliitis despite treatment with NSAIDs, bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy is conditionally recommended*. This recommendation is conditional based on very low quality of supporting evidence and known risks of glucocorticoid treatment. Bridging therapy with oral glucocorticoids may have the most utility in the setting of high disease activity, limited mobility, and/or significant symptoms.

PICO C.6. *In children and adolescents with active sacroiliitis despite treatment with NSAIDs, intraarticular glucocorticoid injection of the sacroiliac joints as adjunct therapy is conditionally recommended*. This recommendation was conditional based on very low quality of evidence and on varying parent and patient preferences regarding the procedure.

PICO C.7. *In children and adolescents with sacroiliitis who have or are at risk for functional limitations, using PT is conditionally recommended*. This recommendation was conditional based on the very low quality of supporting evidence and Voting Panel experience. It was also discussed that there may be a role for PT and activity modification in specifically identifying and reducing mechanical factors contributing to microtrauma and repetitive stress that could potentially contribute to disease activity in these patients (104).

Recommendations for the treatment of JIA and enthesitis (Table 6)

PICO D.1. *In children and adolescents with JIA and active enthesitis, NSAID treatment is* ***strongly*** *recommended over no treatment with an NSAID*. This recommendation is strong despite the very low quality of supporting evidence based on Voting Panel experience, established analgesic effects, and data from adult disease showing benefit (105).

PICO D.2, D.3. *In children and adolescents with JIA and active enthesitis despite treatment with NSAIDs, using a TNFi is conditionally recommended over methotrexate or sulfasalazine*. This recommendation is conditional based on the low quality of supporting evidence. While TNFi is preferred, the Voting Panel discussed that a trial of methotrexate or sulfasalazine may be warranted for patients with contraindications to TNFi, patients with mild enthesitis, and patients with concomitant active peripheral polyarthritis (80,90–95,100).

PICO D.4. *In children and adolescents with JIA and chronic active enthesitis despite treatment with NSAIDs, bridging therapy with a limited course of oral glucocorticoids (<3 months) during initiation or escalation of therapy is conditionally recommended*. This recommendation is conditional based on very low quality of supporting evidence and known risks of glucocorticoid treatment in the pediatric population. Bridging therapy with glucocorticoids may have most utility in the setting of high disease activity, limited mobility, and/or significant symptoms.

PICO D.5. *In children and adolescents with JIA and enthesitis who have or are at risk for functional limitations, using PT is conditionally recommended*. This recommendation was conditional based on very low quality of evidence and Voting Panel experience.

DISCUSSION

This guideline includes 39 recommendations for the treatment of children with JIA and non-systemic polyarthritis, sacroiliitis, and enthesitis. The quality of most of the available evidence was low or very low in relation to the relevant clinical PICO questions, resulting in 31 of the recommendations being conditional.

These recommendations provide an updated approach to the treatment of children with non-systemic polyarthritis, sacroiliitis, and enthesitis. These populations were chosen for this guideline because they have been the focus of significant recent research, with better delineation of the underlying biology and additional treatments available since the 2011 ACR recommendations for JIA. Similar to the 2011 recommendations, this guideline defined patient populations by clinical phenotypes rather than ILAR categories. This decision was made because data continue to suggest that current JIA categories may not accurately reflect the underlying biology and anticipated treatment responses in patients with juvenile arthritis.

This guideline differs from the 2011 recommendations in the definitions of risk factors and disease activity assessment used to generate patient scenarios. Although PICO questions were initially stratified by risk factors and disease activity, the Voting Panel ultimately determined that in most scenarios there were not sufficient data to recommend different treatments for these

patients, and recommendations were frequently combined. Another important difference from the 2011 recommendations is that initial NSAID monotherapy for polyarthritis is no longer recommended, given the established benefits of early initiation of DMARD treatment. Individual PICO questions for each biologic were initially considered but subsequently dropped by the Voting Panel, given mostly equivalent data for safety and efficacy between the biologics and lack of head-to-head comparisons. The exceptions were that TNFi are specifically recommended for sacroiliitis, and rituximab is considered only after TNFi, abatacept, and tocilizumab have been tried. This approach has resulted in a simplified treatment algorithm. Last, this guideline also includes recommendations for escalating care in the setting of low disease activity, highlighting the importance of achieving and maintaining complete disease control, which was not previously addressed.

The current recommendations also differ from the 2011 recommendations in that they were developed using GRADE methodology instead of the RAND/UCLA Appropriateness Method. The systematic, transparent, and explicit process of developing recommendations through GRADE is a major feature accelerating its adoption by professional groups internationally (www.gradeworkinggroup.org). Important features of this method are 1) specification of the patient groups, interventions, competing alternatives, and outcomes so that each recommendation is clearly focused on a particular clinical situation; 2) grading of the quality of evidence; and 3) basing the strength of recommendations on the quality of evidence, balance of benefits and harms, and patient values and preferences for different treatment options. This guideline considered parent and patient preferences assessed by a separate Parent and Patient Panel. Primary themes that emerged from that discussion were: 1) the importance of shared decision-making; 2) the importance of parents and patients receiving information regarding not only the preferred medication or intervention but also the alternatives; and 3) parent/patient support of earlier consideration of biologics given their experiences with decreased adverse effects and improved quality of life with the use of these medications relative to their experiences with methotrexate. Although this was a select group of parents and patients, and their experiences may not be representative of all patients, their discussion provided an important perspective that was incorporated into the Voting Panel discussion and voting.

A topic of particular debate among the Voting Panel was the appropriateness of the use of biologics as initial therapy in children with polyarthritis, particularly for those with risk factors. Ultimately, non–biologic DMARD therapy was recommended, but it was noted that there may be some patients for whom initial biologic therapy is indicated. This remains an area of active research, and currently ongoing studies may better clarify which patients are most likely to benefit from initial biologic therapy. Importantly, studies in pediatrics are underway or planned for a number of new medications, including JAK inhibitors and IL-17 and IL-12/23 inhibitors, and these medications may become useful additions as treatment options for JIA, particularly in patients with sacroiliitis for whom limited options exist. Other studies currently underway in parallel adult diseases may also inform the optimal treatment of enthesitis and the treatment of peripheral spondyloarthritis. Future guideline efforts may determine where these treatments fit into the treatment algorithm and will incorporate the results from the ongoing studies once complete.

Nonpharmacologic interventions addressed in this guideline included PT and OT. In each case, very limited data were identified, and future research in these modalities will be helpful in identifying patients most likely to benefit from these interventions and which modalities have most effectiveness for particular clinical scenarios.

The cJADAS-10 was used to provide general disease activity parameters for defining low and moderate/high disease activity. However, this is not intended to be prescriptive and should be interpreted within the overall clinical context. Furthermore, because the JADAS is a relatively new disease activity measurement tool, new cutoffs may be proposed, since additional data are generated that may accommodate different numbers of active joints or other levels of physician's or parent's global assessment. The identification of valid and practical disease activity measures in JIA remains an important research agenda in pediatric rheumatology. Nevertheless, it was agreed by the Voting Panel that treatment should be escalated in patients with even 1 active joint. Formal recommendations regarding disease activity measurement tools, cutoffs, and monitoring intervals were not specifically addressed in this guideline. Last, the management of inactive disease and the tapering and withdrawal of medications for patients with inactive disease are not addressed in this guideline but will be important for future guidelines.

Because the quality of evidence was overall low and most recommendations were conditional, clinicians, caregivers, and patients should use a shared decision-making process when considering these recommendations. While these recommendations are intended to address common clinical situations, all treatment decisions must be individualized, with consideration of the unique aspects of each patient's presentation, medical history, and preferences.

ACKNOWLEDGMENTS

We thank Alexei Grom, MD, Ron Laxer, MD, FRCP, Mindy Lo, MD, PhD, Sampath Prahalad, MD, MSc, Meredith Riebschleger, MD, Angela Byun Robinson, MD, MPH, Grant Schulert, MD, PhD, Heather Tory, MD, and Richard Vehe, MD, for serving on the Expert Panel. We thank Suzanne Schrandt with the Arthritis Foundation for her involvement throughout the guideline development process. We thank our patient representative for adding valuable perspectives. We thank Liana Fraenkel, MD, MPH, for leading the Patient Panel meeting, as well as the patients and

parents who participated in this meeting: Linda Aguiar, Jake Anderson, Samantha Bell, Julianne Capron, Stephanie Dodunski, Holly Dwyer, Stephanie Kweicein, Carolina Mejia Pena, and Nikki Reitz, LCSW. We thank the American College of Rheumatology staff, including Regina Parker for assistance in organizing the face-to-face meetings and coordinating the administrative aspects of the project, and Robin Lane for assistance with manuscript preparation. We thank Janet Waters for help in developing the literature search strategy and performing the literature search and updates, and Janet Joyce for peer-reviewing the literature search strategy.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ringold had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ringold, Angeles-Han, Beukelman, Lovell, Cuello, Becker, Colbert, Feldman, Ferguson, Gewanter, Guzman, Horonjeff, Nigrovic, Schneider, Halyabar, Turner, Reston.

Acquisition of data. Ringold, Angeles-Han, Beukelman, Lovell, Cuello, Becker, Colbert, Feldman, Ferguson, Gewanter, Guzman, Horonjeff, Nigrovic, Ombrello, Passo, Rabinovich, Schneider, Halyabar, Hays, Shah, Sullivan, Szymanski, Turgunbaev, Reston.

Analysis and interpretation of data. Ringold, Angeles-Han, Beukelman, Lovell, Cuello, Becker, Colbert, Feldman, Ferguson, Gewanter, Guzman, Horonjeff, Nigrovic, Ombrello, Passo, Stoll, Schneider, Halyabar, Hays, Shah, Sullivan, Turgunbaev, Reston.

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Arthritis Care & Research
Vol. 71, No. 6, June 2019, pp 703–716
DOI 10.1002/acr.23871
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SPECIAL ARTICLE

2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis

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Objective. To develop recommendations for the screening, monitoring, and treatment of uveitis in children with juvenile idiopathic arthritis (JIA).

Methods. Pediatric rheumatologists, ophthalmologists with expertise in uveitis, patient representatives, and methodologists generated key clinical questions to be addressed by this guideline. This was followed by a systematic literature review and rating of the available evidence according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. A group consensus process was used to compose the final recommendations and grade their strength as conditional or strong.

Results. Due to a lack of literature with good quality of evidence, recommendations were formulated on the basis of available evidence and a consensus expert opinion. Regular ophthalmic screening of children with JIA is recommended because of the risk of uveitis, and the frequency of screening should be based on individual risk factors. Regular ophthalmic monitoring of children with uveitis is recommended, and intervals should be based on ocular examination findings and treatment regimen. Ophthalmic monitoring recommendations were strong primarily because

This article is published simultaneously in *Arthritis & Rheumatology*.

Supported by the American College of Rheumatology and the Arthritis Foundation. Dr. Angeles-Han's work was supported by the NIH (grant K23-EY-021760 from the National Eye Institute), the Rheumatology Research Foundation, and the Cincinnati Children's Hospital Medical Center Research Innovation and Pilot fund. Drs. Colbert and Ombrello's work was supported by the NIH (grants AR-041184 and AR-041198, respectively, from the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases). Dr. Ferguson's work was supported by the NIH (grant AR-059-703). Dr. Nigrovic's work was supported by the Fundación Bechara. Dr. Sen's work was supported by the Intramural Research Program of the National Eye Institute, NIH (grant EY-000356-16).

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of concerns of vision-threatening complications of uveitis with infrequent monitoring. Topical glucocorticoids should be used as initial treatment to achieve control of inflammation. Methotrexate and the monoclonal antibody tumor necrosis factor inhibitors adalimumab and infliximab are recommended when systemic treatment is needed for the management of uveitis. The timely addition of nonbiologic and biologic drugs is recommended to maintain uveitis control in children who are at continued risk of vision loss.

Conclusion. This guideline provides direction for clinicians and patients/parents making decisions on the screening, monitoring, and management of children with JIA and uveitis, using GRADE methodology and informed by a consensus process with input from rheumatology and ophthalmology experts, current literature, and patient/parent preferences and values.

INTRODUCTION

Uveitis is the most common extraarticular manifestation of juvenile idiopathic arthritis (JIA) and can be a chronic or acute disease. Chronic anterior uveitis (CAU) develops in 10–20% of children with JIA, is usually asymptomatic, and there is rarely external evidence of inflammation (1,2). Acute anterior uveitis (AAU) is a distinctly different form of uveitis. It is typically associated with HLA–B27 and occurs in children with spondyloarthritis (i.e., those with enthesitis-related or psoriatic arthritis). AAU differs from CAU in that AAU is episodic, unilateral, characterized by the sudden onset of erythema, pain, and photophobia, and generally does not require systemic treatment (3).

Uncontrolled CAU can lead to sight-threatening complications such as synechiae, cataracts, and glaucoma in 25–50% and vision loss in 10–20% of children with uveitis (2,4–6). Early detection through regular ophthalmic screening with timely and appropriate treatment can improve visual outcomes and prevent complications (5,7).

Because CAU is often asymptomatic until ocular complications arise, the American Academy of Pediatrics (AAP) published recommendations in 2006 for routine ophthalmic screening in children with arthritis (8). These recommendations were based on an older arthritis nomenclature and did not include uveitis screening in all JIA categories such as psoriatic, enthesitis-related, and undifferentiated arthritis. To fill this gap, in 2012, Heiligenhaus and colleagues from the German Uveitis in Childhood Study Group ("German recommendations") proposed ophthalmic screening schedules based on the International League of Associations for Rheumatology (ILAR) JIA classification scheme (9). These 2 publications, however, did not address the monitoring of children with an established diagnosis of uveitis or the treatment of uveitis. Thus, recommendations for both monitoring and treatment of uveitis in children with JIA are needed.

Initial treatment of children with JIA-associated uveitis typically includes topical glucocorticoids. In those who are refractory to or dependent on topical glucocorticoids, there are no accepted North American guidelines for the use of systemic immunosuppressive therapy. Methotrexate is the usual first-line systemic immunosuppressive agent, followed by tumor necrosis factor inhibitor (TNFi) biologics, particularly the monoclonal antibodies infliximab and adalimumab (10). Despite the frequency with which these drugs are used for uveitis, only 1 large randomized controlled trial (RCT) studying children with JIA-associated uveitis has been published (11). Guidance is needed for the acceptable duration and frequency of topical glucocorticoids prior to initiation of nonbiologic disease-modifying antirheumatic drugs (DMARDs) and systemic biologic therapy, and for the approach to initiation, escalation, and modification of systemic therapy. Optimization of treatment strategies is crucial to improve vision outcomes.

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Dr. Beukelman has received consulting fees from Bristol-Myers Squibb, Sobi, UCB, and Novartis (less than $10,000 each). Dr. Lovell has received consulting fees from AstraZeneca, Amgen, Abbott, Wyeth Pharmaceuticals, Pfizer, Hoffmann-La Roche, Novartis, UCB, Takeda, Janssen, GlaxoSmithKline, Boehringer Ingelheim, Celgene, Bristol-Myers Squibb, and AbbVie (less than $10,000 each). Dr. Nigrovic has received consulting fees from Bristol-Myers Squibb, Pfizer, AbbVie, Novartis, and Sobi (less than $10,000 each) and research grants from Sobi, Novartis, AbbVie, and Genentech (support of the FROST study of systemic JIA through CARRA). Dr. Stoll has received speaking fees from Novartis (less than $10,000). Dr. Rabinovich has received consulting fees from AbbVie (less than $10,000). Dr. Schneider has received consulting fees from Novartis and Sobi (less than $10,000 each). No other disclosures relevant to this article were reported.

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Submitted for publication August 31, 2018; accepted in revised form February 27, 2019.

To address this need, the American College of Rheumatology (ACR) and the Arthritis Foundation (AF) convened expert panels of pediatric rheumatologists and ophthalmologists to develop the first ACR/AF recommendations for the screening, monitoring, and treatment of JIA-associated CAU and AAU. Recognizing the importance of close collaboration and communication between pediatric rheumatologists and ophthalmologists, this guideline was developed in collaboration with experts from both specialties. Patient and parent panels also provided input. Overall, clinicians, parents, and patients should use a shared decision-making process that considers patients' preferences and values. Recommendations for the treatment of children with JIA manifesting as non-systemic polyarthritis, sacroiliitis, and enthesitis were developed concomitantly and are presented separately (12).

METHODS

Methodology overview. This guideline followed the ACR guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process uses the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (www.gradeworkinggroup.org) to rate the quality of the available evidence and to develop the recommendations (13–15). ACR policy guided disclosures and the management of potential conflicts of interest (participant disclosures are available at https://www.rheumatology.org/Portals/0/Files/JIA-Guideline-Disclosures.pdf). Supplementary Appendix 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract) presents the full methods in detail.

Guideline development teams. This work involved 5 groups: 1) a Core Leadership Team, consisting of 4 pediatric rheumatologists, supervised and coordinated the project and drafted the clinical questions and manuscript; 2) a Literature Review Team, led by an experienced literature review consultant, completed the literature search and data abstraction; 3) an Expert Panel, composed of 9 pediatric rheumatologists and 1 ophthalmologist with expertise in the management of uveitis in children, developed the clinical Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions and decided on the scope of the guideline project; 4) a Voting Panel, including 15 pediatric rheumatologists, 2 ophthalmologists, both of whom were uveitis specialists, and 2 adult

Table 1. Terms, definitions, and medication interventions*

Terms/medications	Definition/name
Terms	
Controlled uveitis	Inactive OR grade <1+ anterior chamber cells without new complications due to active inflammation per Standardization of Uveitis Nomenclature criteria†
Complications due to active inflammation‡	New development of peripheral anterior synechiae, posterior synechiae, inflammatory membranes, or cystoid macular edema
Additional signs of active inflammation	Fresh keratic precipitates, increased flare, and hypotony
Complications representing cumulative damage	Cataract, glaucoma/elevated intraocular pressure, hypotony, or sequelae of keratic precipitates (hyalinized spots or ghost keratic precipitates)§
Loss of control‡	Increase of anterior chamber cells to grade 1+ or more or new signs of inflammation/complications of inflammation†
New uveitis activity	No history of prior uveitis or loss of control of previously controlled uveitis
Systemic therapy	Nonbiologic DMARDs and biologics
Medications included in the guideline	
Glucocorticoids	Topical eye drops
	Systemic (all oral)
Nonbiologic DMARDs	Methotrexate
	Leflunomide
	Mycophenolate
	Cyclosporine
Biologic DMARDs	Monoclonal TNF inhibitor (adalimumab, infliximab)
	Etanercept
	Abatacept
	Tocilizumab

* DMARDs = disease-modifying antirheumatic drugs; TNF = tumor necrosis factor.
† Grade 1+ anterior chamber cells = 6–15 cells per field in a 1-mm × 1-mm slit beam.
‡ Loss of control of uveitis, active uveitis, and complications can lead to partial or permanent vision loss.
§ These are not reversible changes and should not be indications to change treatment in the absence of active inflammation.

patients with JIA, assisted with developing the scope of the project and refining PICO questions, reviewed the collated evidence, and voted on the recommendations; and 5) a Parent and Patient Panel, consisting of 9 adult patients with JIA and 2 parents of children with JIA and uveitis, reviewed the collated evidence and provided input on their values and preferences, within the context of a separate voting meeting. Supplementary Appendix 2 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract) presents rosters of the team and panel members. In accordance with ACR policy, the principal investigator and the leader of the Literature Review Team were free of potential conflicts of interest, and in all teams, >50% of the members were free of potential conflicts of interest.

PICO question development and importance of outcomes. The Core Leadership Team drafted the initial project scope, key principles, and relevant clinical PICO questions. These were then presented to the guideline development groups for their review at a scoping face-to-face meeting in which the project plan was defined. GRADE criteria provided the framework for judging the overall quality of evidence (13).

During the scoping meeting, the guideline scope, key terms, and definitions were discussed and agreed upon (Table 1). The Expert Panel chose the following 3 areas of focus: 1) ophthalmic screening for uveitis in children with JIA, 2) ophthalmic monitoring of established uveitis in children with JIA, and 3) use of topical and systemic glucocorticoids and systemic immunosuppressant medications to treat uveitis. This guideline pertains to children with JIA and either CAU or AAU. The Expert Panel defined "controlled uveitis" as an inactive OR grade of <1+ anterior chamber (AC) cells without new complications due to active inflammation per Standardization of Uveitis Nomenclature (SUN) criteria (16). "Loss of control" of uveitis was defined as an increase of AC cells to grade 1+ or more or new signs of inflammation/complications of inflammation. A grade of 1+ AC cells is 6–15 cells/field in a 1-mm × 1-mm slit beam, as seen through a biomicroscope. The term "new uveitis activity" included either new activity in patients with no history of uveitis or recurrent activity in patients with loss of control of previously controlled uveitis. Complications due to active inflammation, additional signs of active inflammation, and complications representing cumulative damage were also defined (Table 1). Loss of control of uveitis, active uveitis, and complications can lead to partial or permanent vision loss.

Critical and important outcomes varied based on the type of recommendation (Table 2). Critical outcomes related to screening included new diagnosis of uveitis and new diagnosis of uveitis with any ocular complications (Table 2). Critical outcomes related to monitoring included loss of control of uveitis and new complications due to inflammation. Critical outcomes related to medication use included loss of control of uveitis, incidence of loss of control of uveitis (rate or frequency of loss of control of uveitis, i.e., number of episodes over time), control of uveitis at 1 month and 3 months, new glucocorticoid-related ocular complications (cataracts, glaucoma/increased intraocular pressure [IOP], infection), and new ocular complications due to inflammation, incident uveitis, and recurrence of uveitis. Other important outcomes for monitoring were severity and level of inflammation and for medication use were side effects of systemic therapy, time to control of uveitis, and time to loss of control of uveitis.

Table 2. Critical and important outcomes*

Type of recommendation	Outcome
Screening	
Critical outcomes	New diagnosis of uveitis
	New diagnosis of uveitis with ANY ocular complications
Monitoring	
Critical outcomes	Loss of control of uveitis
	New complications due to inflammation
Important outcomes	Severity/level of inflammation
Treatment	
Critical outcomes	Loss of control of uveitis
	Incidence of loss of control of uveitis
	Control of uveitis at 1 month and 3 months
	New ocular glucocorticoid complications (cataracts, glaucoma/increased intraocular pressure, infection)
	New ocular complications due to inflammation
	Incident uveitis
	Recurrence of uveitis
Important outcomes	Side effects of systemic therapy
	Time to control of uveitis
	Time to loss of control of uveitis

* Vary depending on the recommendation.

Synthesis of the literature and grading of the evidence. Systematic searches of the published English language literature included OVID Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from inception through June 12, 2017 (see Supplementary Appendix 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract); updated searches were conducted on October 13, 2017. DistillerSR software (https://dis-

tillercer.com/products/distillersr-systematic-reviewsoftware/) (Supplementary Appendix 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract) facilitated duplicate screening of literature search results. Reviewers entered extracted data into RevMan software (http://tech.cochrane.org/revman) and evaluated the risk of bias of primary studies using the Cochrane risk of bias tool (http://handbook.cochrane.org/). RevMan files were exported into GRADEpro software to formulate a GRADE summary of a table showing the GRADE summary of findings (see Supplementary Appendix 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract) for each PICO question (17).

When data were available, the evidence summaries included the benefits and harms for outcomes of interest across studies, the relative effect (with effect size and 95% confidence interval), the number of participants, and the absolute effects. We rated the quality of evidence (also called certainty) for each critical and important outcome as high, moderate, low, or very low quality, taking into account risk of bias, inconsistency, indirectness, imprecision, and other considerations as per the GRADE recommendations.

Moving from evidence to recommendations. GRADE methodology specifies that panels make recommendations based on the balance of benefits and harms, the quality of the evidence (i.e., confidence in effect estimates), and parents/patients' values and preferences. Deciding on the balance between desirable and undesirable outcomes requires estimating the relative value patients place on those outcomes. When the literature did not provide clear evidence, recommendations were based on the values/preferences input from the members of the Parent and Patient Panel and on the experience of the Voting Panel members (including physicians and the 2 patients present).

Consensus building. The Voting Panel voted on the direction and strength of the recommendation related to each PICO question. Recommendations required a 70% level of agreement; if 70% agreement was not achieved during an initial vote, Voting Panel members held additional discussions before re-voting, including rewording of recommendations if needed, until consensus was attained (18). For all conditional recommendations, a written explanation is provided, describing the reasons for this decision and conditions under which the alternative may be preferable. A second round of voting occurred after the face-to-face meeting for recommendations with additional questions. In some instances, the Voting Panel combined PICO questions into 1 recommendation for clarity. Some PICO questions were dropped during the consensus meeting due to insufficient evidence to make a formal recommendation (see Supplementary Appendix 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23871/abstract).

Moving from recommendations to practice. These recommendations are designed to help health care providers work with parents/patients in selecting therapies. Health care providers and parents/patients must take into consideration all active disease domains, comorbidities, and the patient's functional status when choosing the optimal therapy for an individual patient.

RESULTS/RECOMMENDATIONS

The literature searches retrieved 1,704 initial citations, 131 duplications were removed, and 1,537 unique uveitis citations were identified. Full-length articles were abstracted and graded for evidence related to the 34 PICO questions. The available evidence was very low-quality for all PICO questions, mainly because of the lack of evidence and the indirectness of the evidence. Most articles were based on observational studies, which are considered to be low-quality in the GRADE system.

How to interpret the recommendations

1. A *strong recommendation* means that the Voting Panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion would not want to follow the recommendation. Due to the risk of ocular complication with resultant vision loss with irregular or infrequent monitoring, and because ophthalmic examinations are low-risk, all recommendations on ophthalmic monitoring examinations of children with uveitis were strong despite the very low quality of evidence. Patients were concerned about the consequences of infrequent monitoring and agreed there was little disadvantage to monitoring, including the potential cost and inconvenience of frequent visits.
2. A *conditional recommendation* means the Voting Panel believed that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of patient preference and lack of strong evidence, conditional recommendations are preference-sensitive and always warrant a shared decision-making approach. All of the treatment recommendations were conditional, except for 1 related to tapering topical glucocorticoids (Recommendation 18).
3. All of the recommendations had a very low quality of evidence; thus, most of the recommendations are conditional.
4. All of the recommendations are meant to apply to children with JIA at risk of and with associated uveitis, *regardless of activity of arthritis and other manifestations of JIA*.
5. When deciding on the frequency of ophthalmic monitoring and treatment, close collaboration and communication be-

Table 3. Recommendations for ophthalmic screening, ophthalmic monitoring, and treatment of children with JIA-associated uveitis*

Recommendation
Recommendations for ophthalmic screening
In children and adolescents with JIA at high risk of developing uveitis:†
• Ophthalmic screening every 3 months is conditionally recommended (Recommendation 1, PICO 1).
Recommendations for ophthalmic monitoring
In children and adolescents with JIA and controlled uveitis who are:
• Tapering or discontinuing topical glucocorticoids, ophthalmic monitoring within 1 month after each change of topical glucocorticoids is ***strongly*** recommended over monitoring less frequently (Recommendation 2, PICO 3). • On stable therapy, ophthalmic monitoring no less frequently than every 3 months is ***strongly*** recommended over monitoring less frequently (Recommendation 3, PICO 2). • Tapering or discontinuing systemic therapy, ophthalmic monitoring within 2 months of changing systemic therapy is ***strongly*** recommended over monitoring less frequently (Recommendation 4, PICO 4).
Recommendations for glucocorticoid use
In children and adolescents with JIA and active CAU:
• Using prednisolone acetate 1% topical drops is conditionally recommended over difluprednate topical drops (Recommendation 5, PICO 10). • Adding or increasing topical glucocorticoids for short-term control is conditionally recommended over adding systemic glucocorticoids (Recommendation 6, PICO 11).
In children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for uveitis control:
• If not on systemic therapy, adding systemic therapy in order to taper topical glucocorticoids is conditionally recommended over not adding systemic therapy and maintaining topical glucocorticoids only (Recommendation 8, PICO 7). • If still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for at least 3 months and on systemic therapy, changing or escalating systemic therapy is conditionally recommended over maintaining current systemic therapy (Recommendation 9, PICO 8).
In children and adolescents with JIA who develop new CAU activity despite stable systemic therapy:‡
• Topical glucocorticoids prior to changing/escalating systemic therapy is conditionally recommended over changing/escalating systemic therapy immediately (Recommendation 7, PICO 12).
Recommendations for DMARDs and biologics
In children and adolescents with JIA and active CAU who are/have:
• Starting systemic treatment for uveitis, using subcutaneous methotrexate is conditionally recommended over oral methotrexate (Recommendation 10, PICO 13). • Starting a TNFi, starting a monoclonal antibody TNFi is conditionally recommended over etanercept (Recommendation 12, PICO 15). • Severe active CAU and sight-threatening complications, starting methotrexate and a monoclonal antibody TNFi immediately is conditionally recommended over methotrexate as monotherapy (Recommendation 11, PICO 22). • Inadequate response to one monoclonal TNFi at standard JIA dose, escalating the dose and/or frequency of the monoclonal TNFi to above standard is conditionally recommended over switching to another monoclonal antibody TNFi (Recommendation 13, PICO 20). • Failed a first monoclonal antibody TNFi at above-standard dose and/or frequency, changing to another monoclonal antibody TNFi is conditionally recommended over a biologic in another category (Recommendation 14, PICO 21). • Failed methotrexate and 2 monoclonal antibody TNFi at above-standard dose and/or frequency, abatacept or tocilizumab are conditionally recommended as biologic DMARD options, and mycophenolate, leflunomide, or cyclosporine as alternative nonbiologic options (Recommendation 15, PICO 23).
Recommendations for education about and treatment of AAU
In children and adolescents with spondyloarthritis:
• ***Strongly*** recommend education regarding the warning signs of AAU for the purpose of decreasing delay in treatment, duration of symptoms, or complications of iritis (Recommendation 16, PICO 32). • Well controlled with systemic immunosuppressive therapy (DMARD, biologics) who develop an isolated short-lived episode of AAU, conditionally recommend against switching systemic immunosuppressive therapy immediately in favor of treating with topical glucocorticoids first (Recommendation 17, PICO 34).

(continued)

Table 3. (*Cont'd*)

Recommendation
Recommendations for tapering therapy for uveitis
In children and adolescents with JIA and CAU that is controlled on systemic therapy but remain on 1–2 drops/day of prednisolone acetate 1% (or equivalent):
• Tapering topical glucocorticoids first is ***strongly*** recommended over systemic therapy (Recommendation 18, PICO 6).
In children and adolescents with JIA and uveitis that is well controlled on DMARD and biologic systemic therapy only:
• Conditionally recommend that there be at least 2 years of well-controlled disease before tapering therapy (Recommendation 19, PICO 29).

* Each recommendation had very low quality level of evidence. JIA = juvenile idiopathic arthritis; PICO = Patient/Population, Intervention, Comparison, and Outcomes; CAU = chronic anterior uveitis; DMARDs = disease-modifying antirheumatic drugs; TNFi = tumor necrosis factor inhibitor; AAU = acute anterior uveitis.
† High-risk children are those with oligoarthritis, polyarthritis (rheumatoid factor negative), psoriatic arthritis, or undifferentiated arthritis who are also antinuclear antibody positive, younger than 7 years of age at JIA onset, and have JIA duration of 4 years or less.
‡ Definition of new CAU activity: no prior uveitis or loss of control of previously controlled uveitis.

tween rheumatology and ophthalmology subspecialists is crucial. Points to consider include degree of ocular inflammation, presence of complications, use of topical glucocorticoids, and level of IOP.

6. Recommendations on topical glucocorticoids pertain to prednisolone acetate 1% or equivalent dosing with other types of topical glucocorticoids.
7. Recommendations on systemic therapy pertain to nonbiologic DMARDs and biologics and not systemic glucocorticoids.
8. Recommendations that consider TNFi biologics pertain to etanercept, adalimumab, and infliximab only. Monoclonal antibody TNFi refers to adalimumab and infliximab, due to lack of data and experience with other agents (golimumab, certolizumab, or biosimilars) for uveitis in pediatric patients. Only adalimumab, infliximab, etanercept, abatacept, and tocilizumab were discussed, because data on the use of other biologics for treatment of uveitis are lacking.

Recommendation for ophthalmic screening of children with JIA (Table 3 and Figure 1A)

Recommendation 1. *In children and adolescents with JIA at high risk of developing uveitis, ophthalmic screening every 3 months is conditionally recommended over screening at a different frequency.*

The Voting Panel agreed with combining the screening recommendations of the AAP Sections on Rheumatology and Ophthalmology and the German Uveitis in Childhood Study Group (German recommendations) (8,9). AAP recommendations are based on the older classification scheme "juvenile rheumatoid arthritis," which does not include ILAR categories of psoriatic JIA, enthesitis-related arthritis, and undifferentiated arthritis. The screening schedule suggested by the German recommendations incorporates these categories and recommends screening high-risk children every 3 months, similar to the AAP recommendations. Based on the combined AAP and German recommendations, high-risk children are those with oligoarthritis, polyarthritis (rheumatoid factor negative), psoriatic arthritis, or undifferentiated arthritis who are also antinuclear antibody (ANA) positive, younger than 7 years of age at JIA onset, and have JIA duration of 4 years or less. Low- or moderate-risk children are those with high-risk JIA categories but who are ANA negative, age 7 years or older at JIA onset, or have JIA duration of more than 4 years, and those with systemic JIA, polyarthritis (rheumatoid factor positive), and enthesitis-related arthritis. Low- or moderate-risk children should be screened every 6–12 months depending on their combination of risk factors. Because children who have enthesitis-related arthritis or are carrying the HLA–B27 genotype are at risk of both AAU and CAU, they require screening as well. This recommendation was conditional, based on the low quality of evidence, although several reports have described factors that increase the risk of developing uveitis (19–24). Some children have significant eye disease at the time of screening under the current schedule, but there is a lack of data showing that more frequent screening is beneficial. Patients and parents supported the recommended frequency of screening and expressed a desire for frequent screening.

Recommendations for ophthalmic monitoring of children with JIA diagnosed with uveitis (Table 3 and Figure 1B)

Recommendation 2. *In children and adolescents with JIA and controlled uveitis who are tapering or discontinuing topical glucocorticoids, ophthalmic monitoring within 1 month after each change of topical glucocorticoids is* ***strongly*** *recommended over monitoring less frequently.*

Recommendation 3. *In children and adolescents with JIA and controlled uveitis on stable therapy, ophthalmic monitoring*

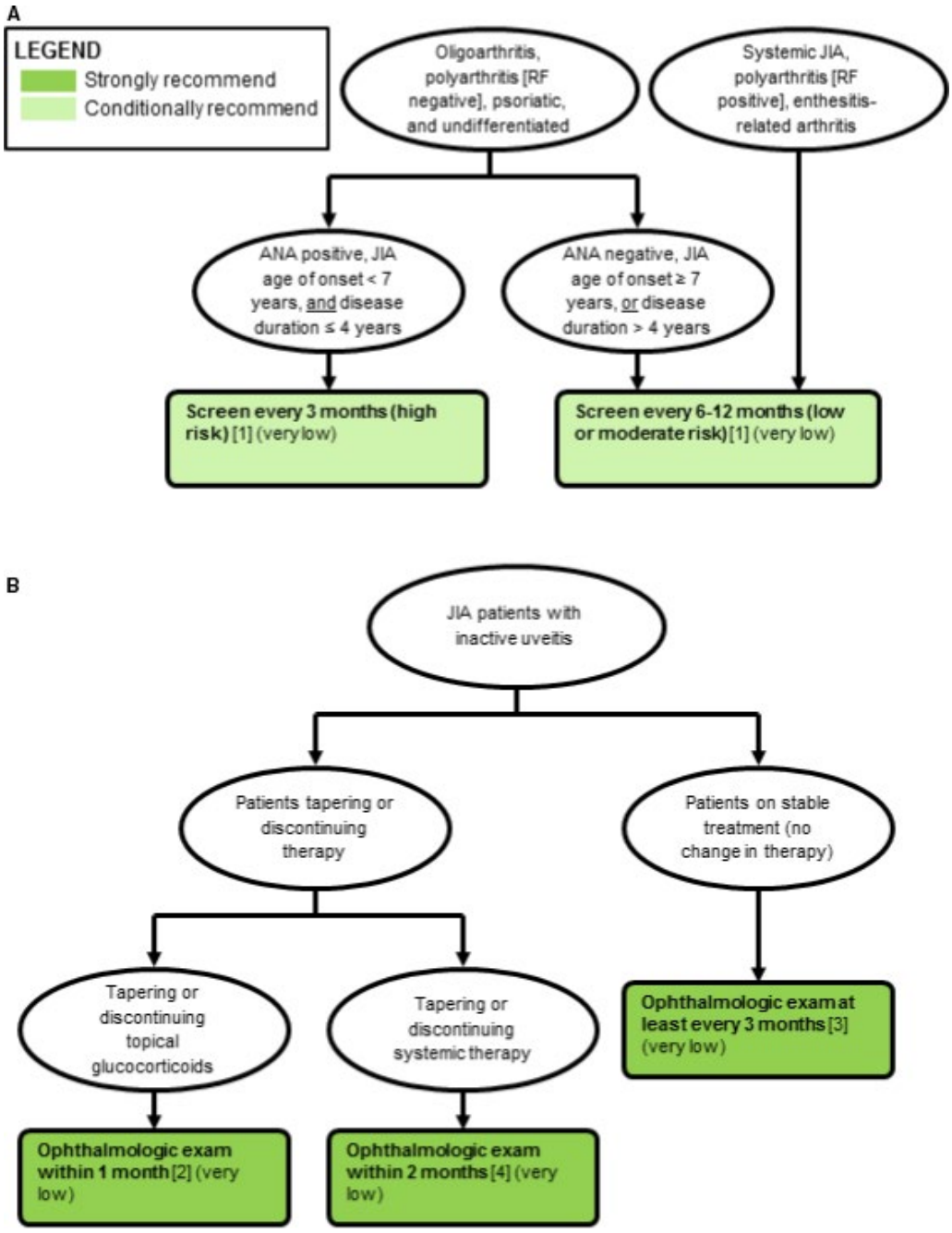

Figure 1. **A,** Ophthalmic screening examinations (see also Table 1). **B,** Ophthalmic monitoring examinations (see also Table 3). No recommendations were made for patients with uncontrolled chronic anterior uveitis. Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions are shown in brackets, and quality of evidence is shown in parentheses. JIA = juvenile idiopathic arthritis; RF = rheumatoid factor; ANA = antinuclear antibody.

no less frequently than every 3 months is ***strongly*** *recommended over monitoring less frequently.*

Recommendation 4. *In children and adolescents with JIA and controlled uveitis who are tapering or discontinuing systemic therapy, ophthalmic monitoring within 2 months of changing systemic therapy is* ***strongly*** *recommended over monitoring less frequently.*

The need for regular monitoring of children with established uveitis was emphasized. The Voting Panel recommends that children with controlled CAU on stable medication should be monitored at 3-month intervals, and those tapering or discontinuing therapy should be monitored at intervals shorter than 3 months, either within 1 month after each change in topical glucocorticoids, and within 2 months of a change in systemic therapy (Figure 1B). Although the quality of evidence was very

low, the recommendations for monitoring were strong due to the potential for harmful consequences of irregular or infrequent monitoring of children with CAU, which could lead to substantial loss of vision and ocular complications from undetected exacerbation of inflammation (20,25). Patients were generally concerned about the consequences of infrequent monitoring and agreed that there was little disadvantage to having frequent ophthalmic examinations. The Voting Panel agreed that the frequency of monitoring may be influenced by the half-life of the systemic therapy and by the expected time for efficacy.

The Voting Panel was not able to reach consensus on a standard schedule of ophthalmic monitoring in children and adolescents with *uncontrolled* CAU; thus, no formal recommendation was made. The Voting Panel agreed, however, that regular monitoring is needed for uncontrolled uveitis, and that in most cases, examinations could occur at 2–6-week intervals tailored to the frequency of topical glucocorticoid administration, IOP, degree of inflammation, and presence of complications, as agreed on by the treatment team.

Recommendations for glucocorticoid use (Table 3 and Figure 2)

Recommendation 5. *In children and adolescents with JIA and active CAU, using prednisolone acetate 1% topical drops is conditionally recommended over difluprednate topical drops.*

Recommendation 6. *In children and adolescents with JIA and active CAU, adding or increasing topical glucocorticoids for short-term control is conditionally recommended over adding systemic glucocorticoids.*

Frequent administration of topical glucocorticoids should be used as initial therapy to control inflammation, followed by tapering as soon as the AC cellular reaction comes under control. The recommendation was conditional based on the very low quality of evidence (26). Prednisolone acetate 1% topical drops are the preferred topical glucocorticoid based on better corneal penetration compared with other eye drops and the fact that there is less experience with difluprednate, which has an increased risk of glucocorticoid-induced IOP and cataract formation (27,28). However, because long-term comparison data between both formulations are lacking, this recommendation was conditional. Patient compliance should be taken into consideration, because prednisolone acetate 1% requires more frequent administration due to its lower potency compared with difluprednate. The Voting Panel recognized that in selected patients, systemic glucocorticoids can be used as short-term bridging therapy. The Voting Panel did not seek consensus to make a recommendation on the use of periocular or intraocular glucocorticoids.

Recommendation 7. *In children and adolescents with JIA who develop new CAU activity despite stable systemic therapy, topical glucocorticoids prior to changing/escalating systemic therapy is conditionally recommended over changing/escalating systemic therapy immediately.*

Initially, topical glucocorticoids should be given to children with uncontrolled uveitis, whether there is a new diagnosis or exacerbation of previously controlled uveitis, unless there is a contraindication. Adding, changing, or escalating (increasing the dose or frequency) systemic therapy should be considered in those children who continue to require prednisolone acetate 1% 1–2 drops/day (or equivalent) (Recommendations 8 and 9). This recommendation was conditional based on very low quality of data.

Recommendation 8. *In children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for uveitis control, and not on systemic therapy, adding systemic therapy in order to taper topical glucocorticoids is conditionally recommended over not adding systemic therapy and maintaining on topical glucocorticoids only.*

The risk of elevated IOP and cataracts increases with greater frequency of administration of topical glucocorticoids (drops/day) and longer duration of therapy. Kothari et al found that topical glucocorticoids at a dosage of ≥2 drops/day was a strong risk factor for IOP elevation, which increased with a greater number of drops daily (29). Another retrospective cohort study showed that ≤3 drops/day of prednisolone is preferred to ≥4 drops/day to decrease the risk of developing cataracts (30). The Voting Panel recommends adding systemic DMARD therapy in children needing ongoing topical glucocorticoids to control uveitis, with the ultimate goal of discontinuation of topical glucocorticoids. These recommendations were conditional due to very low quality of data, and because there may be reasons why a dosage of 1–2 drops/day of topical prednisolone is unacceptable, such as the presence of complications from use of topical glucocorticoids, contraindications to topical glucocorticoids, and difficulty in compliance with multiple drops per day. Nevertheless, prednisolone at a dosage of 1–2 drops/day may be appropriate as monotherapy if there are no issues with ocular complications such as elevated IOP and cataracts, no difficulties with the use of topical glucocorticoids, and there is regular close follow-up with an ophthalmologist.

Recommendation 9. *In children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for at least 3 months and on systemic therapy for uveitis control, changing or escalating systemic therapy is conditionally recommended over maintaining current systemic therapy.*

The Voting Panel agreed on 3 months as the threshold for adding or changing systemic therapy in children who require topical glucocorticoids to maintain uveitis control. Nevertheless, changes in systemic therapy may be warranted earlier, depending on findings on the ocular examination, the duration of topical and systemic therapy, and the presence of existing complications. The recommendation was conditional because of the very low quality of the

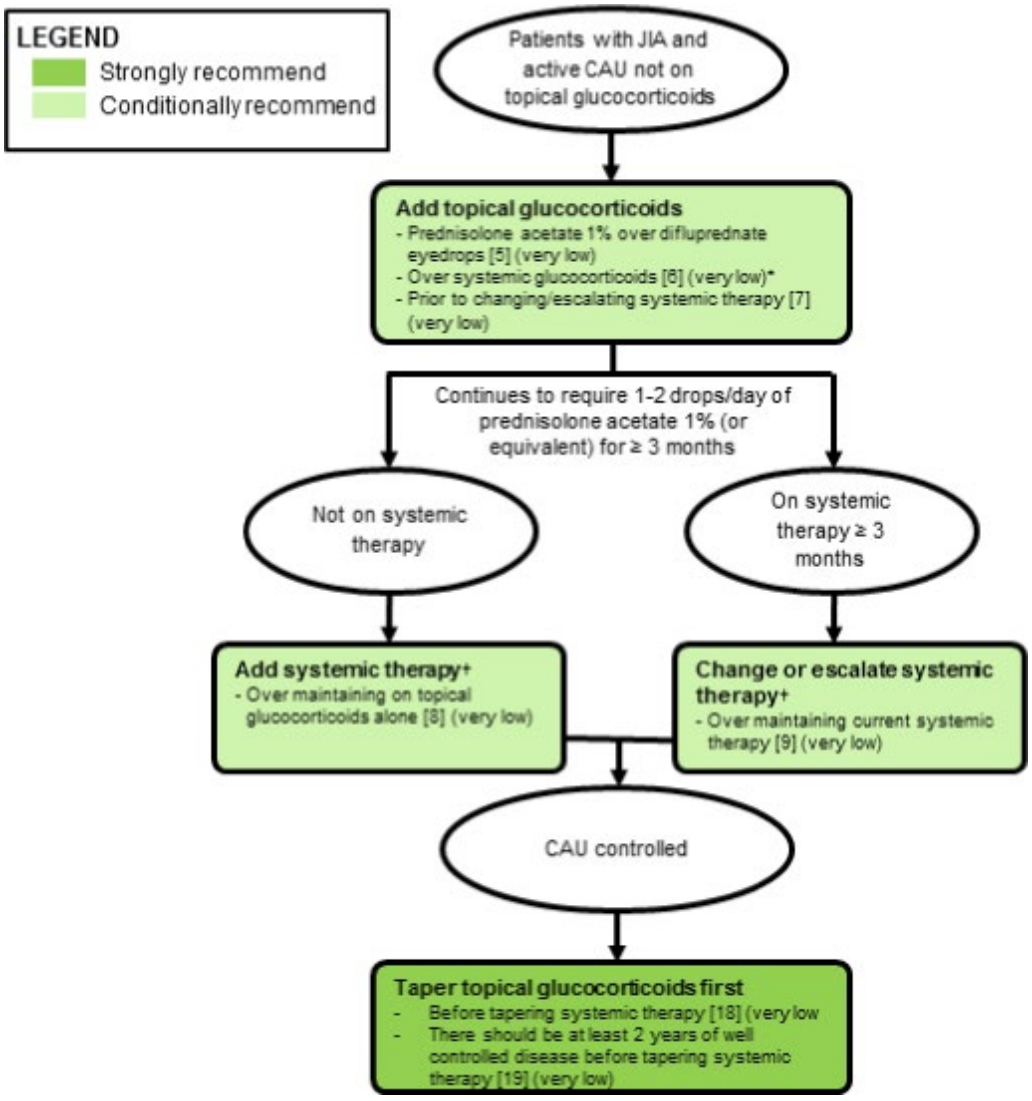
LEGEND
Strongly recommend
Conditionally recommend
Patients with JIA and active CAU not on topical glucocorticoids
Add topical glucocorticoids
- Prednisolone acetate 1% over difluprednate eyedrops [5] (very low)
- Over systemic glucocorticoids [6] (very low)*
- Prior to changing/escalating systemic therapy [7] (very low)
Continues to require 1-2 drops/day of prednisolone acetate 1% (or equivalent) for ≥ 3 months
Not on systemic therapy
On systemic therapy ≥ 3 months
Add systemic therapy+
- Over maintaining on topical glucocorticoids alone [8] (very low)
Change or escalate systemic therapy+
- Over maintaining current systemic therapy [9] (very low)
CAU controlled
Taper topical glucocorticoids first
- Before tapering systemic therapy [18] (very low
- There should be at least 2 years of well controlled disease before tapering systemic therapy [19] (very low)

Figure 2. Recommendations for topical glucocorticoids in patients with juvenile idiopathic arthritis (JIA) and chronic anterior uveitis (CAU) (see also Table 3). Systemic therapy is defined as disease-modifying antirheumatic drugs and biologics. Topical glucocorticoids refer to prednisolone acetate 1% (or equivalent). Doses of prednisolone acetate 1% greater than 1–2 drops/eye/day may be needed initially but increase the risk of ocular complications. Topical glucocorticoids should be used as short-term therapy (≤3 months). The goal is to discontinue topical glucocorticoid use, due to risk of glaucoma and cataracts. Periocular and intraocular injections are administered at the discretion of the treating ophthalmologist. The recommendation numbers are shown in brackets, and quality of evidence is shown in parentheses. * = In selected patients, systemic glucocorticoids can be used as short-term bridging therapy. † = Can escalate dose or frequency of current therapy; 3 months is the threshold for adding or changing systemic therapy in children who require topical glucocorticoids to maintain uveitis control. Changes in systemic therapy may be warranted earlier, depending on findings on the ocular examination, the duration of topical and systemic therapy, and the presence of existing complications.

evidence, the variation in the severity of a child's disease presentation, child and family preference for topical medication over systemic therapy, and the specific systemic therapy being considered.

Recommendations for DMARDS and biologics (Table 3)

Recommendation 10. *In children and adolescents with JIA and CAU who are starting systemic treatment for uveitis, using subcutaneous methotrexate is conditionally recommended over oral methotrexate.*

Recommendation 11. *In children and adolescents with JIA with severe active CAU and sight-threating complications, starting methotrexate and a monoclonal antibody TNFi immediately is conditionally recommended over methotrexate as monotherapy.*

Methotrexate and monoclonal antibody TNFi are the mainstays of systemic treatment of uveitis. Subcutaneous

methotrexate was considered preferable to oral administration for uveitis, but this recommendation was conditional given the lack of strong data on differential efficacy and the notion that family preferences regarding the route of administration may differ. In children with severe active uveitis and sight-threatening complications, combining methotrexate with a monoclonal antibody TNFi at the time of initiation of systemic immunosuppressive treatment was recommended over methotrexate as monotherapy. Severe uveitis could be considered as the presence of ocular structural complications due to uveitis or complications of topical steroid therapy (31). This recommendation was conditional based on the lack of direct evidence from studies, the risk of permanent vision loss, and anticipated differences in patient values and preferences.

Recommendation 12. *In children and adolescents with JIA and active CAU starting a TNFi, starting a monoclonal antibody TNFi is conditionally recommended over etanercept.*

Monoclonal antibody TNFi, specifically adalimumab and infliximab, were conditionally recommended over etanercept for active CAU. Although there is a paucity of direct comparisons, a benefit of using monoclonal antibody TNFi has been shown. The Voting Panel was not able to make recommendations on the preferred TNFi treatment for children with active JIA to prevent uveitis onset or for children with known CAU to prevent uveitis flares, due to lack of evidence (32–36). The Voting Panel also did not make a recommendation on preference between adalimumab and infliximab for use as the initial TNFi.

Recommendation 13. *In children and adolescents with JIA and active CAU who have an inadequate response to 1 monoclonal antibody TNFi at standard JIA dose, escalating the dose and/or frequency to above standard is conditionally recommended over switching to another monoclonal antibody TNFi.*

Recommendation 14. *In children and adolescents with JIA and active CAU who have failed a first monoclonal antibody TNFi at above-standard dose and/or frequency, changing to another monoclonal antibody TNFi is conditionally recommended over a biologic in another category.*

Recommendations 13 and 14 assume that uveitis activity or severity guides therapy in the patient, irrespective of joint disease activity. The Voting Panel did not make a recommendation regarding preference between adalimumab and infliximab as a first-line TNFi or use of above-standard TNFi dosing at treatment initiation.

For children treated with a monoclonal antibody TNFi at standard dosing for patients with JIA who have an inadequate response to therapy, the Voting Panel conditionally recommended escalating the dose and/or frequency to above-standard dosing used for arthritis prior to switching to another monoclonal antibody TNFi. Although consensus was not reached regarding a specific dose or frequency, doses as high as infliximab 20 mg/kg administered every 2 weeks and adalimumab weekly have been reported in observational studies in children with JIA and uveitis (37–39). If treatment with an increased dose/frequency of the initial monoclonal antibody TNFi fails, the recommendation was to change to another monoclonal antibody TNFi prior to changing to a biologic agent in another category. These recommendations were conditional due to the very low quality evidence.

Recommendation 15. *In children and adolescents with JIA and active CAU who have failed methotrexate and 2 monoclonal antibody TNFi at above-standard dose and/or frequency, the use of abatacept or tocilizumab as biologic DMARD options, and mycophenolate, leflunomide, or cyclosporine as alternative nonbiologic DMARD options is conditionally recommended.*

The quality of evidence for subsequent treatment in children who have failed methotrexate in combination with monoclonal antibody TNFi treatment is very low. Based on the current literature, recommended alternative nonbiologic options are mycophenolate mofetil (40), leflunomide (41), or cyclosporine (42), and recommended alternative biologic options are abatacept (43–45) or tocilizumab (46,47); however, evidence supporting preference for a specific nonbiologic or biologic DMARD, combination therapies, and timing of initiation beyond methotrexate, adalimumab, and infliximab is currently lacking. For clarity, several PICO questions were combined in this recommendation.

Recommendations for education about and treatment of acute anterior uveitis (Table 3)

Recommendation 16. *In children and adolescents with spondyloarthritis,* ***strongly*** *recommend education regarding the warning signs of AAU for the purpose of decreasing delay in treatment, duration of symptoms, or complications of iritis.*

AAU is generally a manifestation in a subset of children who are HLA–B27 positive with enthesitis-related arthritis and in some cases of psoriatic arthritis. Although the quality of evidence was very low (no studies addressing these topics were identified), the Voting Panel strongly agreed, based on experience, that HLA–B27–positive patients with enthesitis-related arthritis or psoriatic arthritis and their families should be educated regarding warning signs of AAU, for the purpose of decreasing delay in treatment, duration of symptoms, or ocular complications. Signs include eye pain, redness, and photophobia. This recommendation was strong, because educating about a disease and warning signs is the standard of care.

Recommendation 17. *In children and adolescents with spondyloarthritis otherwise well controlled with systemic immunosuppressive therapy (DMARDs, biologics) who develop AAU, conditionally recommend against switching systemic immunosuppressive*

therapy immediately in favor of treating with topical glucocorticoids first.

Because AAU episodes are typically of short duration and may be easily controlled with topical glucocorticoids, the Voting Panel conditionally recommended continuing the same systemic immunosuppressive therapy and treating with topical glucocorticoids at the initial development of AAU (48). During an isolated short-lived episode of AAU, an immediate escalation or change in underlying systemic therapy may not be necessary without trying a course of topical glucocorticoids first. This recommendation was conditional, because there is a lack of supporting data. Furthermore, frequent recurrent episodes of AAU may prompt a change from a non–monoclonal antibody TNFi to a monoclonal antibody TNFi, or there may be ocular complications from use of topical glucocorticoids that require prompt adjustment of systemic treatment, to decrease exposure to glucocorticoid therapy.

Recommendations for tapering therapy for uveitis (Table 3)

Recommendation 18. *In children and adolescents with JIA and CAU that is controlled on systemic therapy but who remain on 1–2 drops/day of prednisolone acetate 1% (or equivalent), tapering topical glucocorticoids first is* ***strongly*** *recommended over systemic therapy.*

There is very low quality of evidence for timing of tapering of topical glucocorticoids and systemic therapy (25,49,50). Some ophthalmologists feel that in selected cases, it is not possible to discontinue topical glucocorticoids altogether, despite attempts to do so, and the patients may continue to receive 1–2 drops/day for extended periods of time. Despite the very low quality of evidence, the Voting Panel strongly recommended attempting to taper topical glucocorticoids prior to tapering systemic therapy because of the secondary complications that can occur with prolonged and frequent use of glucocorticoids (29,30). Tapering of systemic therapy first may lead to the need for increased frequency of topical glucocorticoids for uveitis flares.

Recommendation 19. *In children and adolescents with uveitis that is well controlled on DMARD and biologic systemic therapy only, conditionally recommend that there be at least 2 years of well-controlled disease before tapering therapy.*

The Voting Panel conditionally recommends attempted tapering of DMARD and biologic systemic therapy only after uveitis has been well controlled for at least 2 years. Relapse-free survival after withdrawal of methotrexate was significantly longer in patients treated with methotrexate for more than 3 years and who had controlled uveitis for more than 2 years before the withdrawal (50). Duration of systemic therapy may be longer than 2 years, because tapering should not begin until at least 2 years of uveitis control. Decisions to taper systemic therapy should also take into consideration other JIA manifestations, including arthritis activity.

DISCUSSION

This 2019 ACR guideline provides direction on the screening of children with JIA at risk of CAU, monitoring of children diagnosed with CAU, treatment with glucocorticoids, nonbiologic DMARDs, and biologic DMARDs for CAU, and education and treatment of children with or at risk of AAU. Few uveitis practice guidelines have a scope this broad (51–54). Although the quality of evidence was very low, and most recommendations were therefore conditional, this guideline fills an important clinical gap in the care of children with JIA-associated uveitis and may be updated as better evidence becomes available.

Optimal care of children with uveitis requires careful and close collaboration among subspecialists, because, in most cases, ophthalmologists assess uveitis activity and ocular complications and provide topical therapy, and rheumatologists manage systemic treatment. Thus, the Voting Panel consisted of both pediatric rheumatologists and ophthalmologists with expertise in uveitis evaluation and management. We acknowledge that there were more pediatric rheumatologists than ophthalmologists on the Voting Panel. However, both ophthalmologists were active in the voting process and in all discussions that led to the final recommendations.

A major limitation is the lack of good-quality evidence in children with JIA and uveitis. Only 1 well-conducted RCT on the use of adalimumab and methotrexate in children with JIA-associated uveitis was identified (11). This highlights the necessity for further studies in this population. We limited our recommendations to biologic DMARDs for which there were sufficient observational data and experience. Thus, biologics such as rituximab, golimumab, certolizumab, TNFi biosimilars, and the nonbiologic drug tofacitinib were not considered. These agents may be included in future guidelines. Although we based our recommendations on studies that focused on the treatment of uveitis specifically, it is difficult to separate treatment of arthritis and CAU in studies. Also, cost was not formally taken into consideration in the guideline. There was heavy reliance on 1 high-quality RCT for the guideline (11), and due to the lack of controlled trial data, most recommendations relied on expert opinion. There is an urgent need for RCTs in children with JIA-associated uveitis, which will better inform treatment decisions in this population. In addition, further investigations are needed on the role of antidrug antibodies, long-term ophthalmic screening in children with JIA, and drug tapering in children with refractory uveitis. As more evidence becomes available, these can inform future guidelines.

In summary, these recommendations provide guidance on the evaluation and management of children at risk of and those with JIA-associated uveitis by rheumatology and ophthalmology

experts, current literature, and patient and parent preferences and values, using state-of-the-art GRADE methodology. Persistent uncontrolled uveitis leads to sight-threatening ocular complications and permanent vision loss. The ultimate goal is to maintain optimal vision and ocular health in children with uveitis by limiting the duration of ocular inflammation, minimizing exposure to long-term topical glucocorticoids through the expedited use of systemic medications, and preventing secondary ocular sequelae.

ACKNOWLEDGMENTS

We thank Alexei Grom, MD, Ron Laxer, MD, FRCP, Mindy Lo, MD, PhD, Sampath Prahalad, MD, MSc, Meredith Riebschleger, MD, Angela Byun Robinson, MD, Grant Schulert, MD, PhD, Heather Tory, MD, and Richard Vehe, MD, for serving on the Expert Panel. We thank Suzanne Schrandt with the Arthritis Foundation for her involvement throughout the guideline development process. We thank our patient representative for adding valuable perspectives. We thank Liana Fraenkel, MD, MPH, for leading the Patient Panel meeting, as well as the patients and parents who participated in this guideline project: Linda Aguiar, Jake Anderson, Samantha Bell, Julianne Capron, Stephanie Dodunski, Holly Dwyer, Stephanie Kweicein, Carolina Mejia Pena, and Nikki Reitz, LCSW. We thank the American College of Rheumatology staff, including Regina Parker for assistance in organizing the face-to-face meetings and coordinating the administrative aspects of the project, and Robin Lane for assistance with manuscript preparation. We thank Janet Waters for help in developing the literature search strategy and performing the literature search and updates, and Janet Joyce for peer-reviewing the literature search strategy.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Angeles-Han had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Angeles-Han, Ringold, Beukelman, Lovell, Cuello, Becker, Colbert, Feldman, Holland, Ferguson, Gewanter, Guzman, Horonjeff, Nigrovic, Ombrello, Passo, Rabinovich, Sen, Schneider, Halyabar, Hays, Shah, Sullivan, Szymanski, Turgunbaev, Reston.

Analysis and interpretation of data. Angeles-Han, Ringold, Beukelman, Lovell, Cuello, Becker, Colbert, Feldman, Holland, Ferguson, Gewanter, Guzman, Horonjeff, Nigrovic, Ombrello, Passo, Stoll, Sen, Schneider, Halyabar, Hays, Shah, Sullivan, Turgunbaev, Reston.

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ARTHRITIS & RHEUMATISM
Vol. 65, No. 10, October 2013, pp 2499–2512
DOI 10.1002/art.38092
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Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and wileyonlinelibrary.com

SPECIAL ARTICLE

2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis

Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.

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INTRODUCTION

The American College of Rheumatology (ACR) published treatment recommendations for juvenile idiopathic arthritis (JIA) in 2011 (1). These recommendations represented the first such effort by the ACR that focused entirely on the treatment of a pediatric rheumatic disease, and included recommendations for the initial and subsequent treatment of patients with synovitis and systemic manifestations and recommendations

This article is published simultaneously in the October 2013 issue of *Arthritis Care & Research*.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

Dr. Ringold's work was supported by the Agency for Healthcare Research and Quality for the duration of this project (grant K12HS019482). Dr. Weiss's work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant 1-K23-AR059749-01A1).

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for medication safety monitoring. Also included in the recommendations was a statement regarding potential areas for a subsequent update. Based on the progress made understanding the pathophysiology of systemic JIA and a rapid increase in data regarding the treatment of systemic JIA and how it differs from other categories of JIA, the ACR determined that the treatment of systemic JIA should be the focus of the first update.

Systemic JIA accounts for approximately 4–15% of JIA and is defined as arthritis in ≥1 joint for at least 6 weeks' duration in a child age <16 years with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days and accompanied by one or more of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly or splenomegaly, and serositis (2). The goal of therapy for systemic JIA is similar to that of the other categories of JIA, and focuses on the prompt control of active inflammation and symptoms and the prevention of a number of disease- and/or treatment-related morbidities such as growth disturbances, joint damage, and functional limitations. Many children with systemic JIA have a particularly refractory course, with persistent disease associated with a high risk of joint damage and severe growth impairment (3–5). However, the inflammatory process underlying systemic JIA appears to be distinct from other categories of JIA, with a central role for both interleukin-1 (IL-1) and IL-6 (6,7). Treatments specifically targeting both of these cytokines are now available, and recently there has been a significant increase in the amount of published data regarding their efficacy. Furthermore, approximately 10% of children with systemic JIA develop overt clinical features of macrophage activation syndrome (MAS), a life-threatening condition characterized by fever, organomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and coagulopathy, among other findings (7–9). The mortality rate for children hospitalized with systemic JIA and MAS is estimated to be as high as 6%, but may even be higher based on estimates from case series (10,11). Systemic JIA is therefore the focus of this update, providing the opportunity to address the treatment of this unique inflammatory process and associated MAS features.

In addition, in response to public comment, this update also includes recommendations for repeat tuberculosis (TB) screening for all categories of JIA patients receiving biologic agents, in order to address questions about followup screening for children receiving these medications for longer durations and the risk of false-positive results associated with annual TB screening performed without regard for risk factors.

As with the previously published ACR recommendations and as specified by the RAND/University of California, Los Angeles (UCLA) Appropriateness Method, cost implications were not considered in assembling these recommendations. The use of combination therapy with a biologic agent was also not considered, due to safety concerns and lack of data. Furthermore, as with the original 2011 ACR JIA treatment recommendations, the results of this project should be considered "recommendations," and are meant to serve as a reference for health care providers caring for children with JIA. These recommendations are not intended to take the place of physician judgment and shared decision making with patients and are not intended to limit the coverage of medications used in the treatment of JIA. Likewise, these recommendations are intended to offer guidance for providers caring for children with the most common phenotypes associated with systemic JIA, rather than exceptional cases with unusual disease manifestations or refractory disease.

A document containing the 2011 ACR JIA treatment recommendations and the 2013 updated recommendations is provided in Supplementary Appendix A

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Dr. Beukelman has received consulting fees from Genentech and McKesson Health Solutions (less than $10,000 each) and from Novartis (more than $10,000). Dr. Ilowite has received consulting fees, speaking fees, and/or honoraria from Janssen and Novartis (less than $10,000 each). Dr. Kimura has received consulting fees, speaking fees, and/or honoraria from Novartis (less than $10,000). Dr. Laxer has received consulting fees, speaking fees, and/or honoraria from Novartis (less than $10,000) and receives royalties from *Textbook of Pediatric Rheumatology*. Dr. Lovell has received consulting fees, speaking fees, and/or honoraria from Novartis and Hoffman-La Roche (less than $10,000 each). Dr. Nigrovic has received consulting fees from Novartis (less than $10,000).

Drs. Ringold and Weiss contributed equally to this work.

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Submitted for publication March 5, 2013; accepted in revised form July 2, 2013.

(available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/art.38092/abstract).

MATERIALS AND METHODS

The ACR reviews its recommendations approximately annually to determine whether a partial update or full revision is warranted, based on changes in supporting evidence and available therapies. In early 2012, the ACR decided that an update to its 2011 JIA recommendations was necessary, specifically in the area of systemic JIA. The ACR leadership subsequently approached the team of investigators who had developed the 2011 JIA guidelines and, through discussions with this group and additional pediatric rheumatologists, assembled a new team to develop the 2013 JIA update.

This project complied with ACR guideline development policies related to disclosure and conflicts of interest. All participants disclosed their relationships at several different points during the process. Disclosures were specifically shared with other participants (e.g., in writing and verbally during meetings), posted online as part of the protocol released for public comment, disclosed during manuscript review, and disclosed in the final manuscript. Per ACR policy, no more than 49% of the Core Expert Panel (CEP) and Task Force Panel (TFP) members had conflicts of interest at any time during this project, and the principal investigators (PIs; SR and PFW) maintained their unconflicted status throughout the project.

The recommendations were developed using the RAND/UCLA Appropriateness Method, which was also used in the development of the 2011 ACR JIA treatment recommendations (1,12). A CEP, consisting of 11 pediatric rheumatologists experienced in the management of JIA and actively involved in JIA research, assisted with refining the scope of this update, developing the literature search strategy and Evidence Report, and finalizing the clinical scenarios. A TFP, consisting of 12 experts in the field of JIA, including participants from Europe and Canada, participated in 2 rounds of voting on the clinical scenarios. Effort was made to include participants from different geographic locations, with variable time since completion of training and different practice focuses. Thirteen of the CEP and TFP participants also had been involved in the development of the 2011 ACR JIA treatment recommendations.

During the voting rounds, members of the TFP rated the appropriateness of each scenario using a 1–9 ordinal scale, as recommended by the RAND/UCLA method (12). Prior to voting, members of the TFP received a Voter's Handbook that included detailed descriptions of the clinical scenarios and voting instructions, and an Evidence Report summarizing results of the systematic review described below. In the first round, the TFP members cast their votes independently by e-mail. At the subsequent face-to-face meeting, TFP members received a summary of the group's anonymous responses for each scenario, with their own individual responses and the group median responses clearly indicated. Discussions at the face-to-face meeting focused primarily on scenarios where there was disagreement among the TFP members, with the goal of the discussion being not to force consensus, but to ensure that all panel members understood and interpreted the scenario and the available evidence in a similar way. A general pediatrician and evidence-based medicine expert and a parent of a child with systemic JIA also participated in the face-to-face meeting discussion to provide additional perspective and input, but did not vote.

Scope of the recommendations. The overarching objective of this project was to update the 2011 ACR recommendations for the use of nonbiologic disease-modifying antirheumatic drugs (DMARDs) and biologic DMARDs in the treatment of systemic JIA. The specific aims of the project were to 1) update the 2011 ACR recommendations regarding indications for starting nonbiologic DMARDs and biologic DMARDs for systemic JIA and indications for switching between nonbiologic DMARDs and biologic DMARDs for systemic JIA; 2) incorporate the use of anti–IL-1 and anti–IL-6 therapies into the ACR recommendations for the treatment of systemic JIA; and 3) develop treatment recommendations for patients with the following 3 general systemic JIA phenotypes: significant systemic features and varying degrees of synovitis, significant arthritis and no significant systemic features, and features concerning for MAS. The aims were specified in the project protocol that was posted online for public comment by the ACR from June to July 2012. In response to public comment, an additional aim was added to the scope to provide recommendations for repeat annual TB screening among children with all categories of JIA who had a negative baseline TB evaluation.

Development of the Evidence Report. *Systematic literature review.* The literature search strategy was developed by the project's PIs (SR and PFW), a medical research librarian, and the CEP. The search strategy underwent peer review by an additional medical librarian using Peer Review of Electronic Search Strategies (13). The search strategies are included in Supplementary Appendix B (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/art.38092/abstract).

The following electronic databases were searched: Ovid MEDLINE, Embase, PubMed, and Cochrane Library (Wiley). For medications included in the 2011 ACR JIA treatment recommendations, these databases were searched from October 6, 2009 (the end date of the literature search for the 2011 ACR JIA treatment recommendations) through July 25, 2012 (Table 1). For medications not included in the 2011 recommendations, the databases were searched from their beginning through July 25, 2012. In addition, each database was searched in its entirety for the treatment of MAS in systemic JIA. The same databases were searched for TB screening and JIA from October 6, 2009 through September 5, 2012.

Conference abstracts were searched for preliminary reports of randomized clinical trials for which the final results were not yet published. Embase was searched for conference abstracts relating to all of the medications included in this update between January 1, 2010 and July 27, 2012. ClinicalTrials.gov was also searched to identify any additional studies with potentially relevant results that were not yet published. Two articles were in submission at the time of the first TFP votes and were included in the Evidence Report, with permission from the authors, to provide the TFP with the most current evidence (14,15). Both articles were in press by the time of the face-to-face meeting, and have subsequently been published.

Table 1. Medications evaluated for the treatment of systemic juvenile idiopathic arthritis*

	2011 recommendations	2013 recommendations
NSAIDs†	X	X
Glucocorticoids	X	X
Methotrexate	X	X
Leflunomide	X	X
IVIG	X	X
Calcineurin inhibitors‡	X	X
TNFα inhibitors§	X	X
Abatacept	X	X
Rituximab	X	X
Anakinra	X	X
Canakinumab		X
Rilonacept		X
Tocilizumab		X

* NSAIDs = nonsteroidal antiinflammatory drugs; IVIG = intravenous immunoglobulin; TNFα = tumor necrosis factor α.
† Includes all NSAIDs commonly used in clinical practice in the US, including selective cyclooxygenase 2 inhibitors.
‡ Cyclosporine and tacrolimus.
§ Adalimumab, etanercept, and infliximab.

An updated search was performed for all sources through January 14, 2013 in order to ensure that more recently published articles were also available for citation. An evaluation of the literature search results was performed by the PIs (SR and PFW) to determine whether any of the newly identified articles would change the recommendations, but none were deemed contradictory to the recommendations made by the TFP, and therefore it was determined that additional consideration of these articles by the TFP was not necessary.

Criteria for study inclusion/exclusion. Studies were included in the Evidence Report if they comprised children (defined as participants ages <18 years) with systemic JIA and if they specifically addressed the treatment of systemic JIA and/or the safety of medications used in this context.

Studies in languages other than English were excluded, as were non-systematic review articles, commentaries, and consensus statements. Articles that reported mechanistic aspects of therapy and did not describe the clinical characteristics of patients or their outcomes were excluded. Studies that assessed only costs were also excluded, as specified by the guideline scope and the RAND/UCLA method.

Development of the Evidence Report. The titles and abstracts of the 2,200 articles identified by the initial search were screened by a panel of volunteers consisting of a medical student, fellows, and junior faculty in pediatric rheumatology (see Acknowledgments), and articles not fulfilling the inclusion criteria were removed. If it was unclear whether an article should be included, it was kept on the list of potentially eligible articles. The full text of each potentially eligible article then underwent additional screening by a volunteer, who gave the article a final determination regarding inclusion/exclusion and extracted relevant data for the Evidence Report. If the reviewer was uncertain about the article's eligibility, the article underwent additional review by one of the PIs (SR), who also reviewed each article's final determination.

A total of 125 articles were included in the final Evidence Report. Three articles were subsequently included from the updated literature search. The data abstracted from each article for the Evidence Report included study design, participants (number and diagnosis), medication (including dose), concurrent medications, inclusion criteria, exclusion criteria, baseline disease measures, primary and secondary outcomes, adverse events, and limitations. If children with different categories of JIA were included in a study, reviewers were asked to document the results for systemic JIA patients separately, whenever possible. The abstracted data were reviewed for clarity and completeness by one of the PIs (SR), and additional data abstraction was performed when needed. Summaries of specific articles from the 2011 Evidence Report were also included in the new report, when relevant. The entire Evidence Report used for the development of the 2011 ACR JIA recommendations was also made available to the TFP members for review, upon request.

Development of the clinical scenarios. Clinical scenarios were developed by the PIs (SR and PFW) with input from the CEP based on the 3 primary phenotypes (see below). The features of poor prognosis and levels of disease activity specified in the 2011 ACR JIA recommendations were not applied to the scenarios in this update based on input from the CEP that these characteristics were of unclear relevance to decision making at the point of care for patients with systemic JIA. The consensus opinion of the CEP was that certain features of poor prognosis (i.e., joint erosions) are often not known or pertinent in new-onset cases. The choice of disease activity variables and their decision thresholds was made using an iterative process via e-mail and teleconferences with repeated revision until they were accepted by all CEP members. For each scenario, there was consensus among CEP members that the disease activity variables included provided a meaningful clinical threshold relevant for treatment decisions. The decision thresholds of active joint count (AJC; $\leq$4 or >4) and physician global assessment (MD global; <5 or $\geq$5) were chosen by CEP consensus. Disease activity descriptors were also limited to restrict the number of scenarios in order to avoid voter fatigue (12). Medication monitoring was not specifically addressed in these scenarios because it was determined that monitoring recommendations for the medications included in this project would not be expected to differ from those of the 2011 ACR JIA recommendations and/or the publicly available recommendations included in the package inserts for each of these medications. Three primary clinical phenotypes were developed. In each case, it was specified that the participants had met the International League of Associations for Rheumatology criteria for systemic JIA at disease onset (2).

For the first phenotype, systemic JIA with active systemic features and varying degrees of synovitis, active systemic features were defined as the presence of any combination of the following disease features: fever, evanescent rash, lymphadenopathy, hepatomegaly, splenomegaly, or serositis. Rather than considering specific combinations of these manifestations, the TFP was asked to consider the treatments among patients with an MD global of <5 or $\geq$5 on a 10-point numerical rating scale and by AJC (0 joints, 1–4 joints, or >4 joints).

For the second phenotype, systemic JIA without active systemic features but with active synovitis, TFP members were

asked to rate the appropriateness of medical therapies based on the total number of active joints (≤4 joints or >4 joints).

For the third phenotype, systemic JIA with features concerning for MAS, features concerning for MAS were defined as any combination of the following disease manifestations: persistent (rather than quotidian) fever, cytopenias or falling cell line counts (particularly platelets), falling erythrocyte sedimentation rate, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis, transaminitis, coagulopathy, organomegaly, low or absent natural killer cell activity, hyperferritinemia, or central nervous system dysfunction. This definition was left intentionally broad given the lack of validated classification criteria for MAS. The scenarios specifically excluded critically ill patients requiring intensive care unit admission.

A separate scenario was developed to address repeat TB screening among all categories of JIA patients receiving biologic agents. The TFP was asked to consider the appropriateness of different screening approaches for TB, including annual screening and risk-based approaches. The TFP did not consider the method of screening (e.g., interferon-γ–release assay versus tuberculin skin test).

Medications, duration of therapy, and doses used in clinical scenarios. The medications addressed in the guideline scenarios are shown in Table 1. For each scenario, it was assumed that prior medications were given for a minimum of 3 months, with the exceptions of 1) anakinra, for which the duration was defined as ≥1 month; 2) nonsteroidal antiinflammatory drug (NSAID) monotherapy, for which the maximum duration was defined as 1 month; and 3) systemic glucocorticoid (GC) monotherapy, for which the maximum duration was defined as 2 weeks. The duration of anakinra was discussed with the CEP at large prior to the TFP voting, and 4 weeks was the timeframe agreed upon for an expected response. The duration of NSAID monotherapy and systemic GC monotherapy was voted on by the TFP.

There was no consideration of combination therapy with a biologic agent. When biologic agents were evaluated as sequential therapy, it was indicated that prior biologic agents were discontinued before initiation of a new one. For the scenarios that addressed the sequential therapy of patients with active systemic features, the TFP voting panel was instructed that these patients could be assumed to be receiving concurrent systemic GC therapy (with the exception of the scenario used to determine the duration of NSAID monotherapy, in which adjunct systemic GCs were specifically excluded) and that they should rate the appropriateness of initiating the medication under consideration either with or without concurrent initiation or increase of GC therapy (whichever approach was considered more appropriate by the voter). Receipt of concurrent GC therapy was not assumed for those scenarios that addressed the treatment of patients without active systemic features but with active synovitis. Tumor necrosis factor α (TNFα) inhibitors were considered together as a single group rather than as individual medications. Different IL-1 inhibitors were considered separately for the scenarios that addressed initiation of the medication because it was determined by the CEP that currently available data could inform this choice. For scenarios that considered IL-1 inhibitors as sequential therapy, these medications were considered as a group rather than separate medications, both to restrict the number of scenarios and because it was determined there would be sparse data to inform the use of a specific IL-1 inhibitor in this situation. For all recommendations, it was also assumed that patients received the typical maximum dose of each medication. Although higher doses of these medications may be appropriate in certain clinical situations, these situations were not specifically considered by the TFP.

In order to limit the number of clinical scenarios on which the TFP would vote, the issue of whether a nonbiologic DMARD and a biologic agent could be combined or whether they would only be used sequentially was left to the provider's discretion.

Rating of the clinical scenarios by the TFP. The TFP members were asked to rate the appropriateness of the interventions in each of the clinical scenario permutations using the Evidence Report, as well as their best clinical judgment. "Appropriateness" was defined as "the health benefits exceed the health risks by a sufficiently wide margin that the intervention is worth doing" (12). The decision to recommend or not recommend initiation of a medication for a particular scenario included the risk of not initiating an alternative therapy (e.g., the risk of initiating drug A includes the risk of not initiating drug B). Each scenario was scored on a numerical rating scale from 1–9, where 1–3 = "inappropriate," 4–6 = "uncertain," and 7–9 = "appropriate." An uncertain score indicated that either the risks or benefits were approximately equal or there was not enough information available for the TFP to make a meaningful evaluation.

Developing recommendations from the TFP votes. The second round of votes from the face-to-face meeting was used to create the final recommendations. Therapies are listed as "recommended" if they met the RAND/UCLA appropriateness definition that includes a median score of 7–9 and no disagreement. Therapies listed as "inappropriate" had a median in the range of 1–3 and no disagreement. Disagreement was defined as at least 3 panelists rating the indication between 1 and 3 and at least 3 panelists rating the indication between 7 and 9. "Uncertain" indications had a median in the range of 4–6 or disagreement regardless of the median score.

Rating of the evidence supporting the final ACR recommendations. Following the development of recommendations, a level of evidence was assigned to each recommendation using the system proposed by the Oxford Centre for Evidence-Based Medicine (16). This is the same rating system used for the 2011 ACR JIA treatment recommendations. Briefly, this rating system creates the following 4 categories for rating evidence: A = randomized controlled trials; B = nonrandomized studies, including retrospective cohort studies; C = uncontrolled studies, including case series; and D = expert opinion. Level B was also assigned to any recommendation for which there was extrapolation from randomized controlled trials. Level C was also assigned to any recommendation for which there was extrapolation from a nonrandomized study or more complex extrapolation from a randomized controlled trial. The level of evidence assigned reflects the highest rating achieved for each recommendation (i.e., if studies in support of a recommendation have a level of evidence ranging from B–D, the overall level of evidence is reported as B). In order to provide the most comprehensive reference list, all relevant

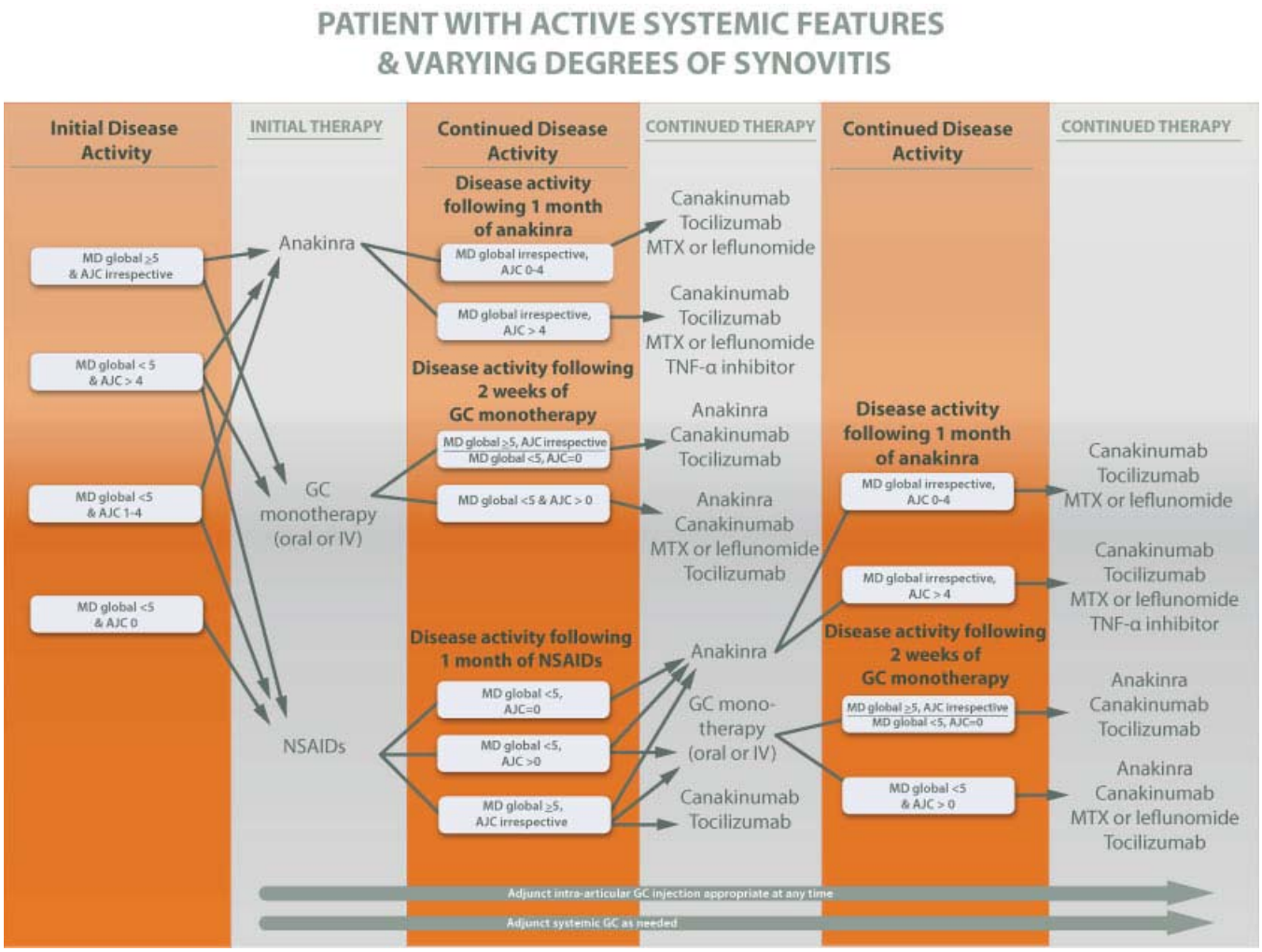

Figure 1. Treatment pathways for patients with active systemic features and varying degrees of synovitis. The Task Force Panel was asked to consider the treatments among patients with active systemic features and a physician global assessment (MD global) of <5 or ≥5 on a 10-point numerical rating scale (0–10 visual analog scale, where 0 = no disease activity and 10 = the most severe) and by active joint count (AJC; 0 joints, 1–4 joints, or >4 joints). If a recommendation is noted to be irrespective of the AJC or MD global, the recommendation was for children with an AJC ≥0 or an MD global >0, respectively. Adjunct systemic glucocorticoids (GCs) and/or intraarticular GCs may be added at any point. Children may qualify for >1 pathway, in which case it is left to the provider's discretion to choose the path they feel is most appropriate based upon specific patient characteristics and/or patient and family preferences. Steps in the progression of therapy can be additive or sequential, except that therapies with a biologic agent are sequential (combination therapy with a biologic agent is not endorsed). The recommendations in this figure are for patients with active systemic features. If the systemic features (but not the arthritis) respond to therapy, then subsequent treatment decisions should be based upon the recommendations in Figure 2. NSAIDs = nonsteroidal antiinflammatory drugs; IV = intravenous; MTX = methotrexate; TNFα = tumor necrosis factor α.

articles from the Evidence Report are cited, even if they did not provide the highest level of evidence.

RESULTS

The recommendations for initiation of various therapeutic agents are listed separately for the following clinical phenotypes of systemic JIA: 1) active systemic features and varying degrees of synovitis, 2) no active systemic features and varying degrees of active synovitis, and 3) features concerning for MAS. Recommended initial therapeutic options are listed first, in alphabetical order. Therapeutic options for continued disease activity after initial therapy are listed next, in alphabetical order. Medications that were considered by the TFP but were

determined to be inappropriate or uncertain (and were not recommended for any of the related scenarios) are listed at the end of each section, in alphabetical order. The assigned level of evidence and corresponding publication citations follow each treatment recommendation. If a recommendation is noted to be irrespective of the AJC or MD global, the recommendation was for children with an AJC ≥0 or an MD global >0, respectively. Continued disease activity, as used in the recommendations below, was defined as an AJC >0 and/or an MD global >0. In some cases, children may qualify for more than one pathway, in which case it is left to the provider's discretion to choose the path they feel is most appropriate based upon specific patient characteristics and/or patient and family preferences.

Systemic JIA with active systemic features and varying degrees of synovitis. The treatment recommendations for this group of patients are shown in Figure 1. The TFP was asked to consider the treatments among patients with an MD global of <5 or ≥5 on a 10-point numerical rating scale and by AJC (0 joints, 1–4 joints, or >4 joints). The TFP voting panel was informed that these patients could be assumed to be receiving concurrent systemic GC therapy and that they should rate the appropriateness of initiating the medication under consideration either with or without concurrent initiation or increase of GC therapy (whichever approach was considered more appropriate by the voter). The recommendations in this section are for patients with active systemic features. If the systemic features (but not the arthritis) respond to therapy, then subsequent treatment decisions should be based upon recommendations in the next section, "Systemic JIA without active systemic features and with varying degrees of active synovitis."

Initial therapeutic options (listed alphabetically). Anakinra was recommended as one initial therapeutic option for patients with an MD global ≥5 irrespective of the AJC, or an MD global <5 and an AJC >0 (level C) (17–19).

Systemic GC monotherapy (administered by oral or intravenous route) was recommended for a maximum period of 2 weeks as a therapeutic option for patients with an MD global <5 and an AJC >4 and for all patients with an MD global ≥5 irrespective of the AJC (level C) (20,21). Continuing GCs as monotherapy for ≥1 month for patients with continued disease activity was inappropriate (level D). The minimum duration of GC monotherapy and specific tapering regimens for GCs were not specifically addressed by the TFP.

Initiating NSAID monotherapy in a patient without prior treatment was recommended as one approach for patients with an MD global <5 irrespective of the AJC (level D). NSAID monotherapy was inappropriate for patients with an MD global ≥5 and an AJC >0 (level D). Continuing NSAID monotherapy for longer than 1 month for patients with continued disease activity was inappropriate (level D). The minimum duration of a trial of NSAIDs was not specifically addressed by the TFP.

Therapeutic options for continued disease activity (listed alphabetically). Use of abatacept was recommended only for patients with an MD global ≥5 and an AJC >4 after a trial of both an IL-1 inhibitor and tocilizumab (sequentially) (level D). Use of abatacept for patients with an AJC of 0 irrespective of the MD global was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it was uncertain. Use of abatacept for patients with an MD global <5 and an AJC >0 or an MD global ≥5 and an AJC <4 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it was uncertain. Use of abatacept for patients with an MD global ≥5 and an AJC >4 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it was appropriate (level D), or patients who had tried a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it was uncertain.

Anakinra was recommended for patients with continued disease activity after treatment with GC monotherapy (level A) (17,18,22–30) or NSAID monotherapy (level C) (17,18,22,28).

Use of a calcineurin inhibitor was recommended only for patients with an MD global ≥5 and an AJC of 0 after a trial of both an IL-1 inhibitor and tocilizumab (sequentially) (level C) (31–36). Use of a calcineurin inhibitor for patients with an MD global <5 and an AJC of 0 was inappropriate (level D), with the exception of patients who received either an IL-1 inhibitor or tocilizumab, in which case it was uncertain. Use of a calcineurin inhibitor for patients with an MD global ≥5 and an AJC of 0 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it was appropriate (level C) (31–36), or patients who had tried an IL-1 inhibitor or tocilizumab, in which case it was uncertain. Use of a calcineurin inhibitor for patients with an AJC >0 irrespective of the MD global was inappropriate (level D), with the exception of patients

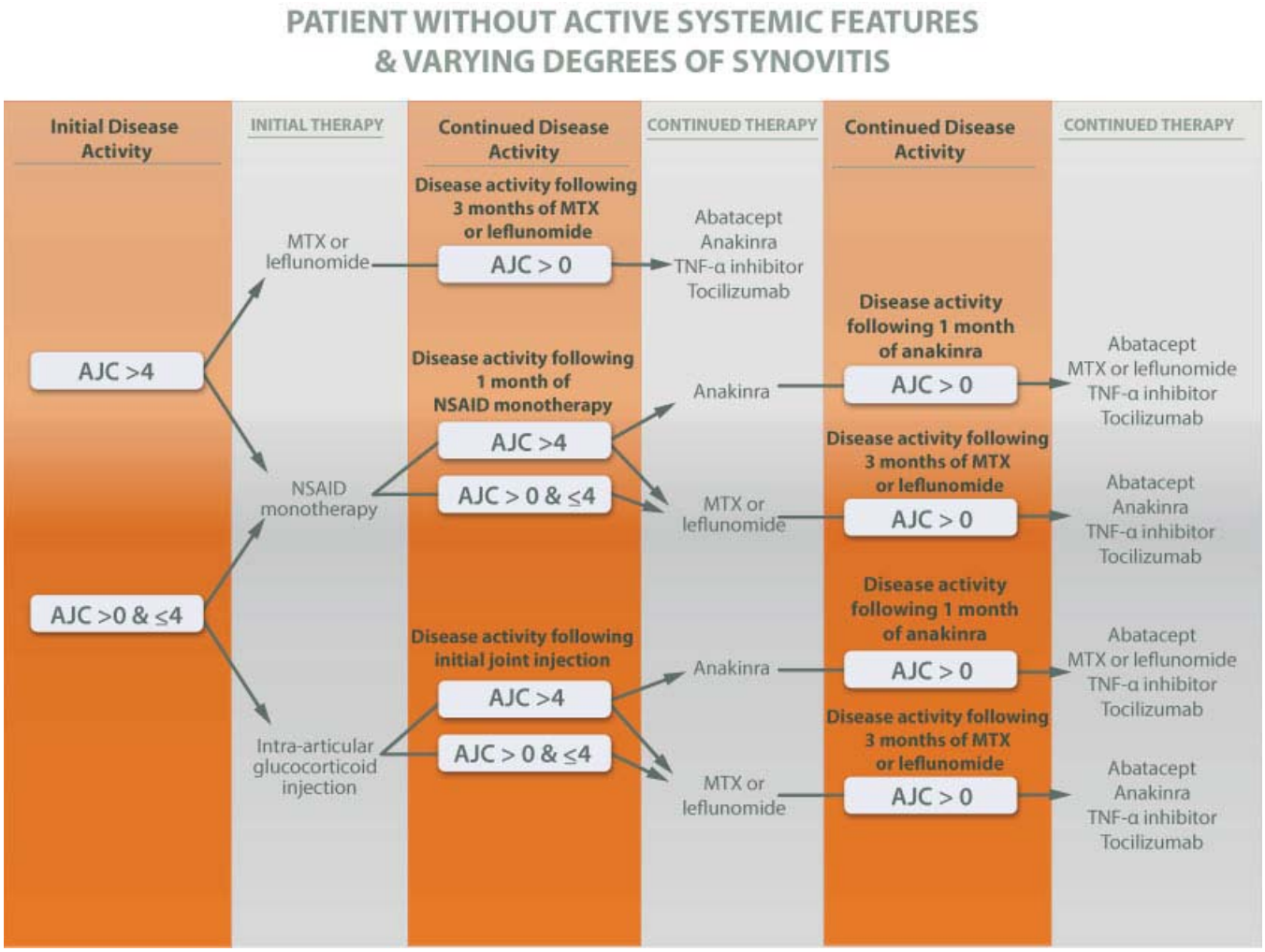

Figure 2. Treatment pathways for patients without active systemic features and with varying degrees of synovitis. The Task Force Panel was asked to rate the appropriateness of therapies based on the total number of active joints (≤4 or >4). Children may qualify for >1 pathway, in which case it is left to the provider's discretion to choose the path they feel is most appropriate based upon specific patient characteristics and/or patient and family preferences. Steps in the progression of therapy can be additive or sequential, except that therapies with a biologic agent are sequential (combination therapy with a biologic agent is not endorsed). AJC = active joint count; MTX = methotrexate; NSAID = nonsteroidal antiinflammatory drug; IV = intravenous; TNFα = tumor necrosis factor α.

who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or an alternate DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it was uncertain.

Canakinumab was recommended for patients with continued disease activity after treatment with GC monotherapy (level A) (14,37), methotrexate (MTX) or leflunomide (level A) (14,37), anakinra (level B) (14,37), or tocilizumab (level C) (14,37) irrespective of the MD global and AJC. Canakinumab was also recommended for patients with an MD global ≥5 irrespective of the AJC, despite prior NSAID monotherapy (level C) (14,37).

GC monotherapy was recommended as an option following failed treatment with NSAID monotherapy for patients with an MD global <5 and an AJC >0 and for patients with an MD global ≥5 irrespective of the AJC (level C) (20,21). Adjunct GC therapy at any point was appropriate to consider (level D).

Intraarticular GC injection was recommended as adjunct therapy at any time (level C) (38,39).

MTX or leflunomide was recommended for pa-

tients with an MD global <5 and an AJC >0 after treatment with GC monotherapy (level C) (40), an IL-1 inhibitor (level D), or tocilizumab (level D). MTX or leflunomide was recommended for patients with an MD global ≥5 and an AJC >0, only after a trial of an IL-1 inhibitor or tocilizumab (level C) (40). Initiation of MTX or leflunomide was inappropriate for patients with an AJC of 0 irrespective of the MD global (level D).

Initiation of a TNFα inhibitor was recommended for patients with an AJC >4 irrespective of the MD global after a trial of an IL-1 inhibitor or tocilizumab (level C) (41,42). Initiation of a TNFα inhibitor was recommended for patients with an AJC >0 irrespective of the MD global after a trial of both an IL-1 inhibitor and tocilizumab (sequentially) (level C) (41,42). Use of a TNFα inhibitor for patients with an MD global <5 and an AJC of 0 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it was uncertain. Use of a TNFα inhibitor for patients with an MD global ≥5 and an AJC of 0 was inappropriate (level D), with the exception of patients who had tried an IL-1 inhibitor or tocilizumab, in which case it was uncertain.

Tocilizumab was recommended as a therapeutic option for patients with continued disease activity following GC monotherapy (level A) (15,43–49), MTX or leflunomide (level B) (15,43–49), or anakinra (level B) (15) irrespective of the MD global and AJC. Tocilizumab was also recommended for patients with an MD global ≥5 irrespective of the AJC despite prior NSAID monotherapy (level C) (15,43–49).

Uncertain or inappropriate options for continued disease activity (listed alphabetically). Use of IVIG was inappropriate irrespective of the AJC and MD global (level D).

Use of nonbiologic DMARD combination therapy (MTX plus leflunomide and/or a calcineurin inhibitor) was uncertain irrespective of the AJC and MD global.

Use of rilonacept was inappropriate as initial therapy irrespective of the MD global and AJC (level D). Use of rilonacept was uncertain for continued disease activity after a trial of other therapeutic options irrespective of the AJC and MD global.

Use of rituximab was inappropriate for patients with an AJC of 0 irrespective of the MD global. Use of rituximab for patients with an MD global <5 and an AJC <4 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it was uncertain. Use of rituximab for patients with an MD global <5 and an AJC >4 or an MD global ≥5 and an AJC >0 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it was uncertain.

Systemic JIA without active systemic features and with varying degrees of active synovitis. The treatment recommendations for this group of patients are shown in Figure 2. The TFP was asked to rate the appropriateness of therapies based on the total number of active joints (≤4 joints or >4 joints). Each of the recommendations below is irrespective of the MD global.

Initial therapeutic options (listed alphabetically). Intraarticular GC injection was recommended as an initial treatment option for patients with an AJC ≤4 (level C) (38,39). Intraarticular GC injection as the only therapeutic intervention was uncertain for patients with an AJC >4. The utility of repeating intraarticular injection as the only intervention was uncertain in a joint or joints currently affected.

Initiation of MTX or leflunomide was recommended for patients with an AJC >4 (level C) (40,50–53).

Initiation of NSAID monotherapy in a patient without prior treatment for a maximum period of 1 month was recommended as one treatment approach for patients with an AJC >0 (level D). Continuing NSAID monotherapy for longer than 2 months for patients with continued disease activity was inappropriate (level D). The minimum duration of a trial of NSAIDs was not specifically addressed by the TFP.

Therapeutic options for continued disease activity (listed alphabetically). Use of abatacept was recommended for patients with an AJC >0 after treatment with MTX or leflunomide (level B) (54–57), anakinra (level D), or tocilizumab (level D).

Anakinra was recommended as a therapeutic option for patients with an AJC >4 following failed intraarticular injection or NSAID monotherapy (level B) (29,58). Use of anakinra was also recommended for patients with an AJC >0 following treatment with MTX or leflunomide (level B) (22,29,30,58).

Initiation of canakinumab was recommended for patients with an AJC >4 only after a trial of a DMARD plus anakinra or tocilizumab (level B) (14,37), a DMARD plus a TNFα inhibitor (level B) (14,37), or abatacept (level C) (14,37).

Use of MTX or leflunomide was recommended as an option for an AJC >0 following treatment with intraarticular injection (level C) (51,52), NSAID monotherapy (level C) (51,52), an IL-1 inhibitor (level D), or tocilizumab (level D).

Initiation of a TNFα inhibitor was recommended for patients with an AJC >0 after treatment with MTX or leflunomide (level C) (59–61), anakinra (level D), or tocilizumab (level D).

Initiation of tocilizumab was recommended for an AJC >0 following treatment with anakinra (level B) (15) or MTX or leflunomide (level B) (15).

Uncertain or inappropriate options for continued disease activity (listed alphabetically). Initiation of nonbiologic DMARD combinations (MTX plus leflunomide and/or a calcineurin inhibitor) was uncertain irrespective of the AJC.

Initiation of rilonacept was uncertain irrespective of the AJC.

Use of rituximab for patients with an AJC ≤4 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD in combination with an IL-1 inhibitor or tocilizumab, in which case it was uncertain. Use of rituximab for patients with an AJC >4 was inappropriate (level D), with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD in combination with an IL-1 inhibitor, tocilizumab, a TNFα inhibitor, or abatacept, in which case it was uncertain.

Systemic JIA with features concerning for MAS. The recommendations for treatment of patients with systemic JIA and features concerning for MAS are described below. These treatment options are not meant to be mutually exclusive and there may be certain clinical situations for which the simultaneous initiation of more than one of these medications is appropriate. Combination therapy with anakinra, a calcineurin inhibitor, and systemic GCs was not specifically addressed.

Initial therapeutic options (listed alphabetically). Use of anakinra was recommended as one therapeutic option for patients with features concerning for MAS (level C) (18,19,28,62–64).

Use of a calcineurin inhibitor was recommended as one therapeutic option for patients with features concerning for MAS (level C) (65–69).

Use of systemic GC monotherapy (administered by oral or intravenous route) was also recommended as a therapeutic option for patients with features concerning for MAS (level C) (70,71). Continuing GC monotherapy for ≥2 weeks in patients with continued features concerning for MAS was inappropriate (level D). Specific tapering strategies for GCs were not specifically addressed by the TFP.

Uncertain or inappropriate options for continued disease (listed alphabetically). Initiation of abatacept was inappropriate (level D).

Use of canakinumab was uncertain, with the exception of patients with an MD global <5 who had received no prior therapy, GC monotherapy, or calcineurin monotherapy, in which case it was inappropriate (level D).

Use of IVIG was inappropriate (level D), with the exception of patients who had tried a calcineurin inhibitor in combination with anakinra, in which case it was uncertain.

Use of MTX or leflunomide was inappropriate (level D).

Use of rilonacept was uncertain.

Use of rituximab was inappropriate (level D).

Use of a TNFα inhibitor was inappropriate irrespective of the MD global (level D), with the exception of patients who had tried a calcineurin inhibitor in combination with anakinra, in which case it was uncertain.

Use of tocilizumab was uncertain.

Repeat testing for latent TB for children with all categories of JIA. Annual screening of children at low risk of TB with an initial negative TB test was inappropriate (level D). It was recommended that patients with an initial negative TB test prior to starting a biologic agent have TB screening repeated at any point if their risk of TB changed to moderate or high, as determined by regional infectious disease guidelines (level D).

DISCUSSION

These recommendations for the treatment of systemic JIA and secondary TB screening are the culmination of a systematic review and formal evaluation of 1,226 scenarios using the RAND/UCLA methodology by an international panel of experts in the field of JIA and pediatric rheumatology, with input from an expert in evidence-based medicine and from the parent of a child with systemic JIA. This current work represents an update of the 2011 ACR JIA treatment recommendations that included recommendations for systemic JIA with systemic features, but due to limitations of data at the time, did not provide recommendations for specific phenotypes of systemic JIA. Since the publication of these initial recommendations, data from randomized trials of new IL-1 inhibitors and IL-6 inhibitors in

children with systemic JIA have been published, supporting the need for updated recommendations including these medications (14,15).

These recommendations should be interpreted in the context of several limitations. First, systemic JIA is a complex disease with heterogeneous manifestations. The phenotypes and scenarios used in the development of these recommendations do not represent all possible patient presentations. The specific influence of disease features such as hip arthritis, rash, and fever was not evaluated; the assumption of the CEP was that fever and other relevant systemic features would be reflected in the MD global. The lack of a standardized disease activity score also limited the development of clinical scenarios, and the categorization of disease severity by the AJC and MD global may also limit the scenarios' representation of the variety of possible patient presentations. The decision thresholds of AJC (≤ 4 or >4) and MD global (<5 and ≥ 5) were chosen by CEP consensus. Their validity may be scrutinized in the future by examining their relationship with therapeutic decisions in standard clinical practice and with criteria for enrolling patients in randomized clinical trials.

Several recommendations were assigned level of evidence A because there was at least one well-designed randomized clinical trial to help inform the recommendation. For example, the level A evidence available to support the use of anakinra after treatment with GC monotherapy for children with active systemic features is the ANAJIS trial, which is a randomized trial, but it is a single trial that enrolled only 24 patients, making it necessary to interpret efficacy and safety data with some caution. The conclusions of ANAJIS are borne out from multiple case series that reached the same conclusion. Furthermore, because many of these recommendations are derived from expert opinion (level of evidence D) rather than higher levels of evidence, these recommendations may require revision as new data are generated regarding treatment efficacy, effectiveness, and safety, and as understanding of the underlying disease pathogenesis expands.

Specifying GC dosing, route of administration, and tapering guidelines is an important endeavor, but was beyond the scope of this project and not amenable to the RAND/UCLA methodology. However, a recent study used consensus methodology to develop an algorithm for standardized GC management in systemic JIA (72). Optimal combinations of DMARD therapies with or without therapies with a biologic agent for the scenarios above are not well understood, and it is anticipated that new data may help to clarify these treatment choices as well. Lastly, although the treatment pathways generated by these recommendations have been simplified as much as possible to facilitate their use in the clinical setting, they remain relatively complex. This complexity reflects the level of discussion and decision making by the TFP and it is anticipated that in the future, with more data available, these pathways may be simplified.

Development of treatment recommendations for children with systemic JIA and features of MAS is particularly challenging. First, there are no diagnostic criteria for MAS complicating systemic JIA, although preliminary criteria were proposed in 2005 and there is an international effort underway to develop these criteria based on expert opinion and analysis of existing patient data (73,74). Second, the etiology of MAS complicating systemic JIA is likely heterogeneous. As such, a specified stepwise treatment algorithm will not work for all patients with this disease. As more is learned about the various etiologies and pathophysiology of MAS in this population of patients, we will hopefully be able to use more targeted and efficacious therapies. The recommendation to use anakinra, calcineurin inhibitors, and GCs is certainly an important first step. However, it is anticipated that in the near future, with more data regarding treatments and a better understanding of the disease process, these recommendations may be modified.

It should be noted that these recommendations do not address the initial screening for TB prior to prescribing immunosuppressive medication, the necessity of which has been clearly established elsewhere (75). These guidelines also do not assess the method of screening, since this is addressed by the American Academy of Pediatrics (AAP) Red Book and by the Centers for Disease Control and Prevention (75,76). Currently, interferon-γ–release testing is not indicated for children ages <5 years. The AAP Red Book does not recommend repeat routine testing for children who remain at low risk while receiving immunosuppressive medication, consistent with the conclusion of the TFP for this project. If the patient history or local epidemiologic factors suggest a possible exposure, immediate and periodic skin testing or interferon-γ–release testing is recommended by the AAP.

These recommendations are distinct from the recently published Childhood Arthritis and Rheumatology Research Alliance (CARRA) systemic JIA consensus treatment plans (CTPs) (77). The CARRA treatment plans reflect the existing diverse treatment practices across North America, are based on nominal

group consensus techniques, and were developed for the purpose of conducting observational comparative effectiveness research. In contrast to these guidelines, the CTPs do not address specific disease phenotypes, and are more restricted in the medications assessed. It is anticipated that data from comparative effectiveness research based upon the CARRA CTPs will likely be very informative in future guidelines projects.

These recommendations, representing the culmination of a rigorous systematic literature review and the use of the RAND/UCLA appropriateness methodology, are an important contribution to the care of children with systemic JIA, offering recommendations to providers caring for children with this challenging disease.

ACKNOWLEDGMENTS

The authors would like to thank Janet Joyce, Amy Miller, and Regina Parker of the ACR for their guidance and administrative support. We would also like to thank the following people for their assistance with screening and abstraction of articles for the development of the Evidence Report: Drs. Abdul Al-Rasheed, Alex Aminoff, Danielle Bennett, Colleen Correll, Lauren Henderson, Patricia Hobday, Ginger Janow, Jennifer Ji Young Lee, Pai-Yue Lu, Melissa Mannion, Theresa Muskardin, Dax Rumsey, Yonit Sterba, Alysha Taxter, and Patricia Vega-Fernandez.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Ringold and Weiss had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ringold, Weiss, Beukelman, DeWitt, Ilowite, Kimura, Laxer, Lovell, Nigrovic, Robinson, Vehe.

Acquisition of data. Ringold, Weiss, Beukelman, Laxer, Lovell, Nigrovic.

Analysis and interpretation of data. Ringold, Weiss, Ilowite, Kimura, Laxer, Nigrovic.

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Arthritis & Rheumatology
Vol. 72, No. 2, February 2020, pp 220–233
DOI 10.1002/art.41142
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2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the clinician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes, but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision, as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

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Objective. To develop an evidence-based guideline for the comprehensive management of osteoarthritis (OA) as a collaboration between the American College of Rheumatology (ACR) and the Arthritis Foundation, updating the 2012 ACR recommendations for the management of hand, hip, and knee OA.

Methods. We identified clinically relevant population, intervention, comparator, outcomes questions and critical outcomes in OA. A Literature Review Team performed a systematic literature review to summarize evidence supporting the benefits and harms of available educational, behavioral, psychosocial, physical, mind-body, and pharmacologic therapies for OA. Grading of Recommendations Assessment, Development and Evaluation methodology was used to rate the quality of the evidence. A Voting Panel, including rheumatologists, an internist, physical and occupational therapists, and patients, achieved consensus on the recommendations.

Results. Based on the available evidence, either strong or conditional recommendations were made for or against the approaches evaluated. Strong recommendations were made for exercise, weight loss in patients with knee and/or hip OA who are overweight or obese, self-efficacy and self-management programs, tai chi, cane use, hand orthoses for first carpometacarpal (CMC) joint OA, tibiofemoral bracing for tibiofemoral knee OA, topical nonsteroidal antiinflammatory drugs (NSAIDs) for knee OA, oral NSAIDs, and intraarticular glucocorticoid injections for knee OA. Conditional recommendations were made for balance exercises, yoga, cognitive behavioral therapy, kinesiotaping for first CMC OA, orthoses for hand joints other than the first CMC joint, patellofemoral bracing for patellofemoral knee OA, acupuncture, thermal modalities, radiofrequency ablation for knee OA, topical NSAIDs, intraarticular steroid injections and chondroitin sulfate for hand OA, topical capsaicin for knee OA, acetaminophen, duloxetine, and tramadol.

Conclusion. This guideline provides direction for clinicians and patients making treatment decisions for the management of OA. Clinicians and patients should engage in shared decision-making that accounts for patients' values, preferences, and comorbidities. These recommendations should not be used to limit or deny access to therapies.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, affecting an estimated 302 million people worldwide (1–5), and is a leading cause of disability among older adults. The knees, hips, and hands are the most commonly affected appendicular joints. OA is characterized by pathology involving the whole joint, including cartilage degradation, bone remodeling, osteophyte formation, and synovial inflammation, leading to pain, stiffness, swelling, and loss of normal joint function.

As OA spans decades of a patient's life, patients with OA are likely to be treated with a number of different pharmaceutical and nonpharmaceutical interventions, often in combination. This report provides recommendations to guide patients and clinicians in choosing among the available treatments. Certain principles of management apply to all patients with OA (see Comprehensive Management of OA below and Figure 1). Some recommendations are specific to a particular joint (e.g., hip, knee, patellofemoral joint, first carpometacarpal joint [CMC]) or particular patient populations (e.g., those with erosive OA).

METHODS

This guideline, from the American College of Rheumatology (ACR) and the Arthritis Foundation (AF), follows the ACR guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of the available evidence and to develop the recommendations (6). ACR policy guided management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Osteoarthritis). A full description of the methods is presented in Supplementary Appendix 1 (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41142/abstract).

Briefly, this work involved 5 teams: 1) a Core Leadership Team that supervised and coordinated the project and drafted the clinical/population, intervention, comparator, outcomes (PICO) questions that served as the basis for the evidence report and manuscript; 2) a Literature Review Team that completed the literature screening and data abstraction and produced the Evidence Report (Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/art.41142/abstract); 3) an Expert Panel that had input into scoping and clinical/PICO question development; 4) a Patient Panel; and 5) an interprofessional Voting Panel that included rheumatologists, an internist, physical and occupational therapists, and patients (Supplementary Appendix 3, http://onlinelibrary.wiley.com/doi/10.1002/art.41142/abstract).

This guideline included an initial literature review limited to English-language publications from inception of the databases to October 15, 2017, with updated searches conducted on August 1, 2018 and relevant papers included. Studies published after August 1, 2018 were not evaluated for this guideline. Supplementary Appendix 4 (http://onlinelibrary.wiley.com/doi/10.1002/art.41142/abstract) shows search terms used and databases reviewed, and Supplementary Appendix 5 (http://onlinelibrary.wiley.com/doi/10.1002/art.41142/abstract) highlights the study selection process. The guideline evidence base results from our own systematic review of randomized

This article is published simultaneously in *Arthritis Care & Research*.

Supported by the American College of Rheumatology and the Arthritis Foundation.

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Dr. Neogi has received consulting fees from Pfizer, Regeneron, EMD Merck Serono, and Novartis (less than $10,000 each). Dr. Hochberg has received consulting fees, speaking fees, and/or honoraria from Bone Therapeutics, Bristol-Myers Squibb, EMD Serono, IBSA, and Theralogix LLC (less than $10,000 each) and from Eli Lilly, Novartis Pharma AG, Pfizer, and Samumed LLC (more than $10,000 each), royalties from Wolters Kluwer for UpToDate, owns stock or stock options in BriOri BioTech and Theralogix LLC, and is President of Rheumcon, Inc. Dr. Block has received consulting fees, speaking fees, and/or honoraria from Zynerba Pharma, GlaxoSmithKline, and Medivir (less than $10,000 each) and royalties from Agios, GlaxoSmithKline, Omeros, and Daiichi Sankyo for human chondrosarcoma cell lines. Dr. Callahan has received consulting fees, speaking fees, and/or honoraria from AbbVie (less than $10,000.) Dr. Kwoh has received consulting fees, speaking fees, and/or honoraria from Astellas, Fidia, GlaxoSmithKline, Kolon TissueGene, Regeneron, Regulus, Taiwan Liposome Company, and Thusane (less than 10,000 each) and from EMD Serono, and Express Scripts (more than $10,000 each). Dr. Nelson has received consulting fees and/or honoraria from Flexion, GlaxoSmithKline, and Medscape (less than $10,000 each). Dr. Samuels has received consulting fees, speaking fees, and/or honoraria from Dinora, Inc. (less than $10,000). Dr. Altman has received consulting fees, speaking fees, and/or honoraria from Flexion, GlaxoSmithKline, Novartis, Olatec, Pfizer, Sorrento Therapeutics, and Teva Pharmaceutical Industries (less than $10,000 each). No other disclosures relevant to this article were reported.

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Submitted for publication July 2, 2019; accepted in revised form October 11, 2019.

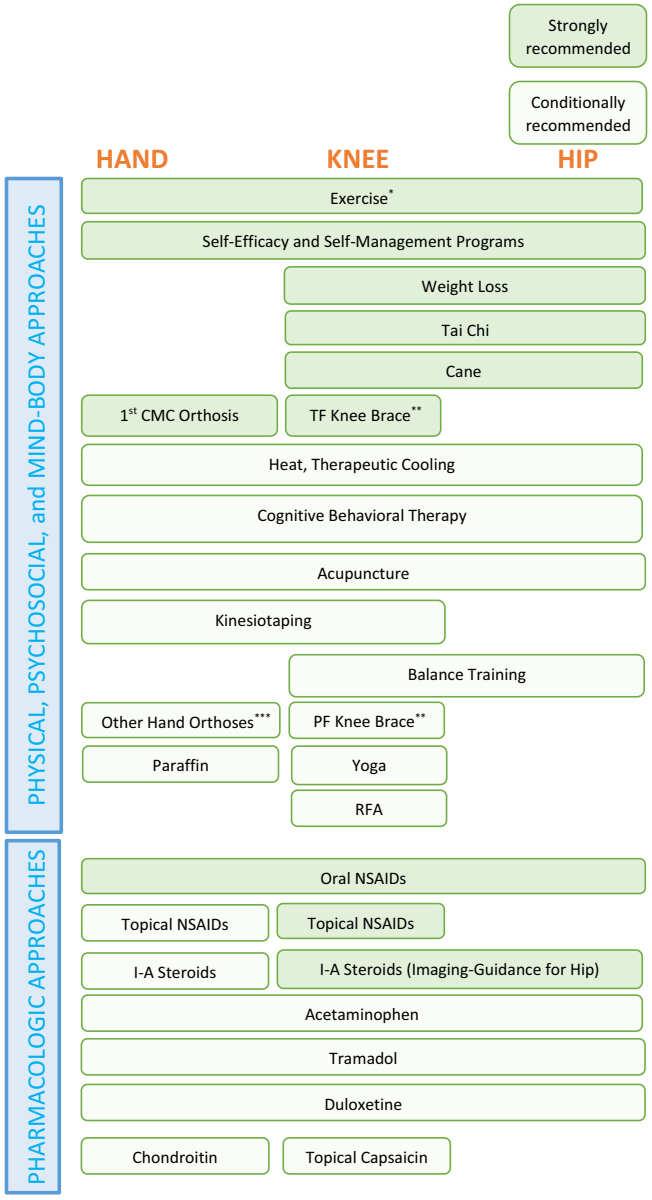

Figure 1. Recommended therapies for the management of osteoarthritis (OA). Strongly and conditionally recommended approaches to management of hand, knee, and/or hip OA are shown. No hierarchy within categories is implied in the figure, with the recognition that the various options may be used (and reused) at various times during the course of a particular patient's disease. * = Exercise for knee and hip OA could include walking, strengthening, neuromuscular training, and aquatic exercise, with no hierarchy of one over another. Exercise is associated with better outcomes when supervised. ** = Knee brace recommendations: tibiofemoral (TF) brace for TF OA (strongly recommended), patellofemoral (PF) brace for PF OA (conditionally recommended). *** = Hand orthosis recommendations: first carpometacarpal (CMC) joint neoprene or rigid orthoses for first CMC joint OA (strongly recommended), orthoses for joints of the hand other than the first CMC joint (conditionally recommended). RFA = radiofrequency ablation; NSAIDs = nonsteroidal antiinflammatory drugs; IA = intraarticular.

controlled trials (RCTs), rather than focusing on systematic reviews and meta-analyses published by others, as was done for the 2012 ACR recommendations for the use of nonpharmacologic and pharmacologic therapies in hand, hip, and knee OA (7). Systematic reviews of observational studies published by others were included if, in the opinion of the Voting Panel, they added critical information for the formulation of a recommendation: for example, related to adverse effects that may not be seen in shorter-duration RCTs. Subsequent updates of this guideline will consider studies included here and new RCTs published since completion of the literature review for the current publication.

Although RCTs are considered the gold standard for evaluation, a number of limitations of RCTs proved particularly important in the formulation of the final recommendations: possible publication bias (favoring publication of positive results), inadequate blinding, and inadequate provision of active comparators and appropriate sham alternatives. Further, short-duration RCTs cannot provide adequate prognostic information when applied to a complex disease such as OA, in which pathophysiologic processes are slowly progressive over decades.

We focused on management options that are available in the US and, for pharmacologic therapies, we additionally focused on agents that are available in pharmaceutical-grade formulations, thus eliminating most nutraceuticals. We limited our review to the English-language literature. We reviewed www.clinicaltrials.gov to identify phase 2 and 3 trials that may be far enough along to be US Food and Drug Administration (FDA)–approved and available by the time this guideline was published.

A hierarchy of outcome measures assessing pain and function in OA was developed based on the published literature (8,9). This hierarchy is detailed in Supplementary Appendix 1 (http://onlinelibrary.wiley.com/doi/10.1002/art.41142/abstract).

Using GRADE, a recommendation can be either in favor of or against the proposed intervention and either strong or conditional (10,11). The strength of the recommendation is based on a 70% consensus among the Voting Panel members. Much of the evidence proved indirect (did not specifically address the PICO question as written) and of low-to-moderate quality (12,13). The Voting Panel made *strong recommendations* when it inferred compelling evidence of efficacy and that benefits clearly outweighed harms and burdens. Thus, a strong recommendation means that the Voting Panel was confident that the desirable effects of following the recommendation outweigh potential undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion of patients would not want to follow the recommendation.

The Voting Panel made *conditional recommendations* when the quality of the evidence proved low or very low and/

or the balance of benefits versus harms and burdens was sufficiently close that shared decision-making between the patient and the clinician would be particularly important. Conditional recommendations are those for which the majority of informed patients would choose to follow the recommended course of action, but some would not (14,15). Thus, conditional recommendations are particularly value- and preference-sensitive and always warrant a full shared decision-making approach involving a complete and clear explication of benefits, harms, and burdens in language and in a context that patients understand (16). Where recommendations are made regarding a particular approach, details and references regarding that approach can be found in the Evidence Report (Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/art.41142/abstract).

RESULTS/RECOMMENDATIONS

Comprehensive management of OA

A comprehensive plan for the management of OA in an individual patient may include educational, behavioral, psychosocial, and physical interventions, as well as topical, oral, and intraarticular medications. Recommendations assume appropriate application of physical, psychological, and/or pharmacologic therapies by an appropriate provider. Goals of management and principles for implementing those goals have broad applicability across patients. However, for some patients at some time points, a single physical, psychosocial, mind-body, or pharmacologic intervention may be adequate to control symptoms; for others, multiple interventions may be used in sequence or in combination. Which interventions and the order in which interventions are used will vary among patients. An overview of a general approach to management of OA is outlined in Figure 1 for recommended options, but no specific hierarchy of one option over another is implied other than on the basis of strength of the recommendation. Figure 2 summarizes the approaches that were not recommended.

Treatment decisions should take the personal beliefs and preferences of the patient, as well as the patient's medical status, into consideration. This guideline applies to patients with OA with no specific contraindications to the recommended therapies. However, each patient should be assessed for the presence of medical conditions, such as hypertension, cardiovascular disease, heart failure, gastrointestinal bleeding risk, chronic kidney disease, or other comorbidities, that might have an impact on their risk of side effects from certain pharmacologic agents, as well as injuries, disease severity, surgical history, and access to and availability of services (transportation, distance, ability to take time off work, cost, insurance coverage) that might have an impact on the choice of physical, psychological, and mind-body approaches. It is assumed that such an assessment

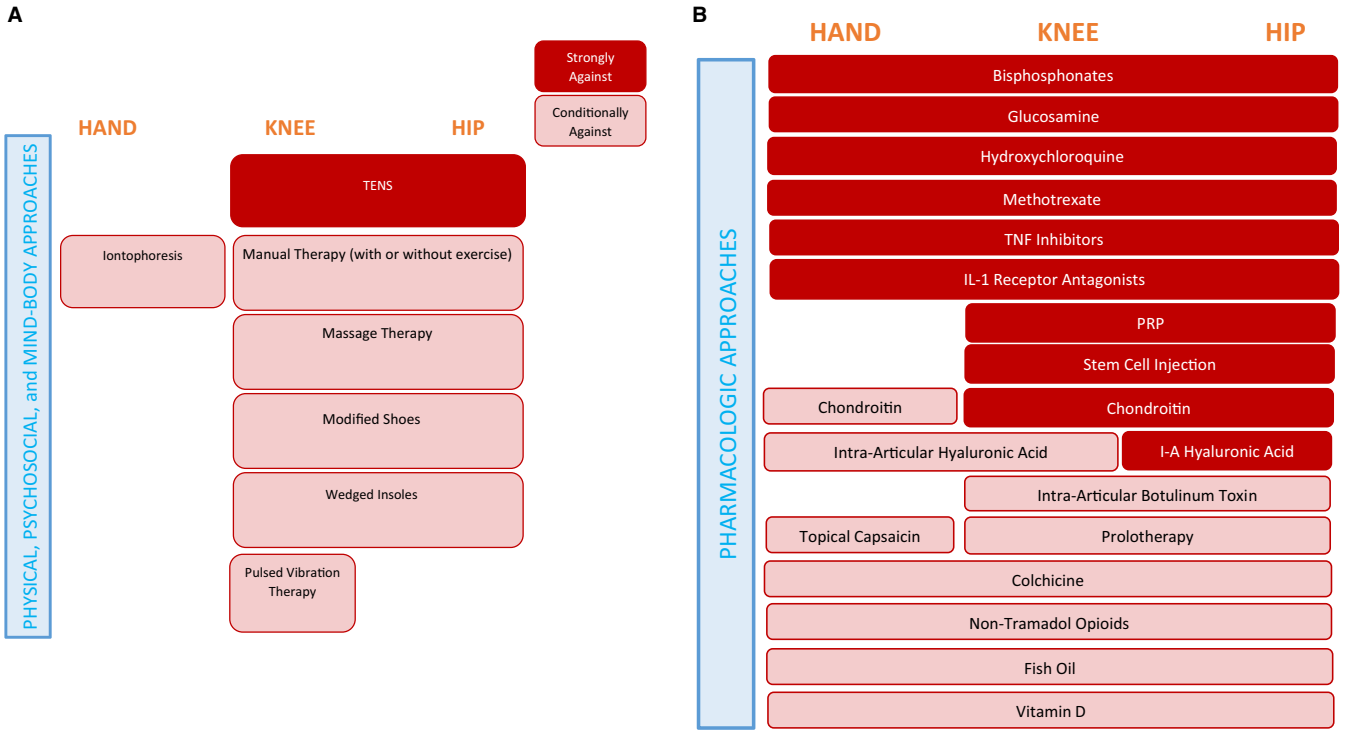

Figure 2. Therapies recommended *against* (physical, psychosocial, and mind-body approaches [**A**] and pharmacologic approaches [**B**]) in the management of hand, knee, and/or hip osteoarthritis. No hierarchy within categories is implied in the figure. TENS = transcutaneous electrical nerve stimulation; TNF = tumor necrosis factor; IL-1 = interleukin-1; PRP = platelet-rich plasma; IA = intraarticular.

will be performed prior to finalization of an individual treatment plan. When choosing among pharmacologic therapies, management should begin with treatments with the least systemic exposure or toxicity.

Patients may experience a variety of additional symptoms as a result of the pain and functional limitations arising from OA and/or comorbidities. These include mood disorders, such as depression and anxiety, altered sleep, chronic widespread pain, and impaired coping skills. The Patient Panel noted that the broader impact of OA on these comorbidities is of particular importance when choosing among treatment options and best addressed by a multimodal treatment plan, rather than one that is limited to the prescription of a single medication. Measures aimed at improving mood, reducing stress, addressing insomnia, managing weight, and enhancing fitness may improve the patient's overall well-being and OA treatment success. Indeed, interventions that have proven beneficial in the management of chronic pain may prove useful in OA (17) even when data specific to patients with OA are limited.

Unless otherwise specified, recommendations regarding physical, psychosocial, and mind-body approaches assume that the patient will be adding the intervention to usual care. For the purposes of this guideline, usual care includes the use of maximally recommended or safely tolerated doses of over-the counter oral nonsteroidal antiinflammatory drugs (NSAIDs) and/or acetaminophen, as has generally been explicitly permitted in clinical trials of nonpharmacologic interventions.

Physical, psychosocial, and mind-body approaches (Table 1)

During the GRADE analysis, clinical trials involving physical modalities and mind-body approaches were often designated as yielding low-quality evidence because blinding with regard to the active treatment was not always possible. This contributed to a preponderance of conditional recommendations for physical modalities and mind-body approaches. The delivery of instruction by physical and occupational therapists is helpful, and often essential, for the appropriate initiation and maintenance of exercise as a part of OA management. In addition to exercise, physical and occupational therapists often incorporate self-efficacy and self-management training, thermal therapies, and instruction in use of and fitting of splints and braces in their practices. Most patients with OA are likely to experience benefit from referral to physical therapy and/or occupational therapy at various times during the course of their disease.

Exercise is strongly recommended for patients with knee, hip, and/or hand OA.

Though exercise is strongly recommended for all OA patients, there is considerably more evidence for the use of exercise in the treatment of knee and hip OA than for hand OA, and the variety of exercise options studied is far greater. While patients and providers seek recommendations on the "best" exercise and the ideal dosage (duration, intensity, and frequency), current evidence

Table 1. Recommendations for physical, psychosocial, and mind-body approaches for the management of osteoarthritis of the hand, knee, and hip

Intervention	Joint		
	Hand	Knee	Hip
Exercise			
Balance training			
Weight loss			
Self-efficacy and self-management programs			
Tai chi			
Yoga			
Cognitive behavioral therapy			
Cane			
Tibiofemoral knee braces		(Tibiofemoral)	
Patellofemoral braces		(Patellofemoral)	
Kinesiotaping	(First carpometacarpal)		
Hand orthosis	(First carpometacarpal)		
Hand orthosis	(Other joints)		
Modified shoes			
Lateral and medial wedged insoles			
Acupuncture			
Thermal interventions			
Paraffin			
Radiofrequency ablation			
Massage therapy			
Manual therapy with/without exercise			
Iontophoresis	(First carpometacarpal)		
Pulsed vibration therapy			
Transcutaneous electrical nerve stimulation			

Strongly recommended
Conditionally recommended
Strongly recommended against
Conditionally recommended against
No recommendation

is insufficient to recommend specific exercise prescriptions. Broad recommendations suggesting one form of exercise over another are based largely on expert opinion. A substantial body of literature (see Evidence Report, Supplementary Appendix 2 [http://onlinelibrary.wiley.com/doi/10.1002/art.41142/abstract]) supports a wide range of appropriate exercise options and suggests that the vast majority of OA patients can participate in, and benefit from with regard to pain and function, some form of exercise. Exercise recommendations to patients should focus on the patient's preferences and access, both of which may be important barriers to participation. If a patient does not find a certain form of exercise acceptable or cannot afford to participate or arrange transportation to participate, he or she is not likely to get any benefit from the suggestion to pursue that exercise.

In the majority of studies that assessed the role of aerobic exercise in the management of OA, walking was the most common form of exercise evaluated, either on a treadmill or as supervised, community-based, indoor fitness walking. Other studies used supervised group cycling on stationary bicycles. Strengthening exercises have included the use of isokinetic weight machines, resistance exercise training with and without props such as elastic bands, and isometric exercise. Neuromuscular training has been developed to address muscle weakness, reduced sensorimotor control, and functional instability specifically seen with knee OA, with a series of dynamic maneuvers of increased complexity. Aquatic exercise often encompasses aspects of aerobic fitness exercises and exercises for enhancing joint range of motion, in a low-impact environment.

A specific hierarchy of these various forms of exercise could not be discerned from the literature. Patient participants on the Patient and Voting Panels raised the concern that patients who are in pain might be hesitant to participate in exercise. There is no uniformly accepted level of pain at which a patient should or should not exercise, and a common-sense approach of shared decision-making between the treating clinician and the patient regarding when to initiate an exercise program is advisable. However, clinical trials of exercise for OA include patients with pain and functional limitations due to OA, and improvements in OA-specific outcomes have been demonstrated; thus, results are likely to be generalizable to most patients with pain due to OA.

Although there is currently insufficient evidence to recommend one form of exercise over another, patients will likely benefit from advice that is as specific as possible, rather than simple encouragement to exercise. Given the wide range of evidence-based exercise interventions shown to effectively improve pain and function in OA, all patients should be encouraged to consider some form of exercise as a central part of their treatment plan. Individual preferences, access, and affordability are likely to play a role in what works best for an individual patient. Overall, exercise programs are more effective if supervised, often by physical therapists and sometimes in a class setting, rather than when performed by the individual at home. They also tend to be more effective when combined with self-efficacy and self-management interventions or weight loss programs.

Few studies have employed monitoring devices or pre- and postintervention assessment of cardiovascular or musculoskeletal fitness, so targets using these devices or assessments are not available. Future research is essential to establish specific exercise guidelines that will direct the patient and provider toward more individualized exercise prescriptions.

Balance exercises are conditionally recommended for patients with knee and/or hip OA.

Balance exercises include those that improve the ability to control and stabilize body position (American Physical Therapy Association: http://www.apta.org/BalanceFalls/). Although one might expect balance exercises to help reduce the risk of falls in patients with OA, RCTs to date have not addressed this outcome in this population, and the low quality of evidence addressing the use of balance exercises necessitates only a conditional recommendation for balance exercises.

Weight loss is strongly recommended for patients with knee and/or hip OA who are overweight or obese.

A dose-response has been noted with regard to the amount of weight loss that will result in symptom or functional improvement in patients with OA (18). A loss of ≥5% of body weight can be associated with changes in clinical and mechanistic outcomes. Furthermore, clinically important benefits continue to increase with weight loss of 5–10%, 10–20%, and >20% of body weight. The efficacy of weight loss for OA symptom management is enhanced by use of a concomitant exercise program.

Self-efficacy and self-management programs are strongly recommended for patients with knee, hip, and/or hand OA.

Although effect sizes are generally small, the benefits of participation in self-efficacy and self-management programs are consistent across studies, and risks are minimal. These programs use a multidisciplinary group–based format combining sessions on skill-building (goal-setting, problem-solving, positive thinking), education about the disease and about medication effects and side effects, joint protection measures, and fitness and exercise goals and approaches. Health educators, National Commission for Certification Services–certified fitness instructors, nurses, physical therapists, occupational therapists, physicians, and patient peers may lead the sessions, which can be held in person or online. In the studies reviewed, sessions generally occurred 3 times weekly, but varied from 2 to 6 times weekly.

Tai chi is strongly recommended for patients with knee and/or hip OA.

Tai chi is a traditional Chinese mind-body practice that combines meditation with slow, gentle, graceful movements, deep diaphragmatic breathing, and relaxation. The efficacy of tai chi may

reflect the holistic impact of this mind-body practice on strength, balance, and fall prevention, as well as on depression and self-efficacy.

Yoga is conditionally recommended for patients with knee OA.

Yoga is a mind-body practice with origins in ancient Indian philosophy and typically combines physical postures, breathing techniques, and meditation or relaxation (National Center for Complementary and Integrative Health [NCCIH]: https://nccih.nih.gov/health/yoga). Though far less well studied than tai chi, yoga may be helpful in OA through a similar blend of physical and psychosocial factors. Due to lack of data, no recommendation can be made regarding use of yoga to help manage symptoms of hip OA. Other mind-body practices could not be assessed due to insufficient evidence, as well as a lack of standard definitions of certain interventions (hypnosis, qi gong).

Cognitive behavioral therapy (CBT) is conditionally recommended for patients with knee, hip, and/or hand OA.

There is a well-established body of literature (19,20) supporting the use of CBT in chronic pain conditions, and CBT may have relevance for the management of OA. Trials have demonstrated improvement in pain, health-related quality of life, negative mood, fatigue, functional capacity, and disability in conditions other than OA. In OA, limited evidence suggests that CBT may reduce pain (21). Further research is needed to establish whether or not benefits in OA are related to alteration in mood, sleep, coping, or other factors that may co-occur with, result from, or be a part of the experience of OA (22).

Cane use is strongly recommended for patients with knee and/or hip OA in whom disease in 1 or more joints is causing a sufficiently large impact on ambulation, joint stability, or pain to warrant use of an assistive device.

Tibiofemoral knee braces are strongly recommended for patients with knee OA in whom disease in 1 or both knees is causing a sufficiently large impact on ambulation, joint stability, or pain to warrant use of an assistive device, and who are able to tolerate the associated inconvenience and burden associated with bracing.

Patellofemoral braces are conditionally recommended for patients with patellofemoral knee OA in whom disease in 1 or both knees is causing a sufficiently large impact on ambulation, joint stability, or pain to warrant use of an assistive device.

The recommendation is conditional due to the variability in results across published trials and the difficulty some patients will have in tolerating the inconvenience and burden of these braces. Optimal management with knee bracing is likely to require that clinicians are familiar with the various types of braces and where they are available and have expertise in fitting the braces. Patient Voting Panel members strongly emphasized the importance of coordination of care between primary care providers, specialists, and providers of braces.

Kinesiotaping is conditionally recommended for patients with knee and/or first CMC joint OA.

Kinesiotaping permits range of motion of the joint to which it is applied, in contrast to a brace, which maintains the joint in a fixed position. Published studies have examined various products and methods of application, and blinding with regard to use is not possible, thereby limiting the quality of the evidence.

Hand orthoses are strongly recommended for patients with first CMC joint OA.

Hand orthoses are conditionally recommended for patients with OA in other joints of the hand.

A variety of mechanical supports are available, including digital orthoses, ring splints, and rigid or neoprene orthoses, some of which are intended for specifically affected joints (e.g., first CMC joint, individual digits, wrist) and some of which support the entire hand. In addition, gloves may offer benefit by providing warmth and compression to the joints of the hand. Data are insufficient to recommend one type of orthosis over another for use in the hand. Patients considering these interventions will likely benefit from evaluation by an occupational therapist.

Modified shoes are conditionally recommended *against* in patients with knee and/or hip OA.

Modifications to shoes can be intended to alter the biomechanics of the lower extremities and the gait. While optimal footwear is likely to be of considerable importance for those with knee and/or hip OA, the available studies do not define the best type of footwear to improve specific outcomes for knee or hip OA.

Lateral and medial wedged insoles are conditionally recommended *against* in patients with knee and/or hip OA.

The currently available literature does not demonstrate clear efficacy of lateral or medial wedged insoles.

Acupuncture is conditionally recommended for patients with knee, hip, and/or hand OA.

Although a large number of trials have addressed the use of acupuncture for OA, its efficacy remains a subject of controversy. Issues related to the use of appropriate blinding, the validity of sham controls, sample size, effect size, and prior expectations have arisen with regard to this literature. Variability in the results of RCTs and meta-analyses is likely driven, in part, by differences in the type of controls and the intensity of the control

interventions used. In addition, the benefits of acupuncture result from the large contextual effect plus small differences in outcomes between "true" and "sham" acupuncture. The latter is of the same magnitude as the effect of full-dose acetaminophen versus placebo. The greatest number of positive trials with the largest effect sizes have been carried out in knee OA. Positive trials and meta-analyses have also been published in a variety of other painful conditions and have indicated that acupuncture is effective for analgesia. While the "true" magnitude of effect is difficult to discern, the risk of harm is minor, resulting in the Voting Panel providing a conditional recommendation.

Thermal interventions (locally applied heat or cold) are conditionally recommended for patients with knee, hip, and/or hand OA.

The method of delivery of thermal interventions varies considerably in published reports, including moist heat, diathermy (electrically delivered heat), ultrasound, and hot and cold packs. Studies using diathermy or ultrasound were more likely to be sham controlled than those using other heat delivery modalities. The heterogeneity of modalities and short duration of benefit for these interventions led to the conditional recommendation.

Paraffin, an additional method of heat therapy for the hands, is conditionally recommended for patients with hand OA.

Radiofrequency ablation is conditionally recommended for patients with knee OA.

A number of studies have demonstrated potential analgesic benefits with various ablation techniques but, because of the heterogeneity of techniques and controls used and lack of long-term safety data, this recommendation is conditional.

Massage therapy is conditionally recommended *against* in patients with knee and/or hip OA.

Massage therapy encompasses a number of techniques aimed at affecting muscle and other soft tissue (NCCIH: https://nccih.nih.gov/health/massage/massageintroduction.htm#hed2). Studies addressing massage have suffered from high risk of bias, have included small numbers of patients, and have not demonstrated benefit for OA-specific outcomes. Patient participants on the Patient and Voting Panels noted that some studies have shown positive outcomes and minimal risk and felt strongly that massage therapy was beneficial for symptom management (23). However, based on the available evidence regarding OA specifically, a conditional recommendation against the use of massage for reduction of OA symptoms is made, though the Voting Panel acknowledged that massage may have other benefits.

Manual therapy with exercise is conditionally recommended *against* over exercise alone in patients with knee and/or hip OA.

Manual therapy techniques may include manual lymphatic drainage, manual traction, massage, mobilization/manipulation, and passive range of motion and are always used in conjunction with exercise (http://guidetoptpractice.apta.org/content/1/SEC38.extract). A limited number of studies have addressed manual therapy added to exercise versus exercise alone in hip and knee OA. Although manual therapy can be of benefit for certain conditions, such as chronic low back pain, limited data in OA show little additional benefit over exercise alone for managing OA symptoms.

Iontophoresis is conditionally recommended *against* in patients with first CMC joint OA.

There are no published RCTs evaluating iontophoresis for OA in any anatomic location.

Pulsed vibration therapy is conditionally recommended *against* in patients with knee OA.

Few trials have addressed pulsed vibration therapy, and in the absence of adequate data, we conditionally recommend against its use.

Transcutaneous electrical stimulation (TENS) is strongly recommended *against* in patients with knee and/or hip OA.

Studies examining the use of TENS have been of low quality with small size and variable controls, making comparisons across trials difficult. Studies have demonstrated a lack of benefit for knee OA.

Pharmacologic management (Table 2)

RCTs of pharmacologic agents may be subject to a variety of limitations, including generalizability of their findings across patients. Publication bias may reduce the likelihood that negative trials will become part of the published literature. Statistically significant findings may represent benefits so small that they are not clinically important to patients. We have highlighted these considerations where relevant.

Topical NSAIDs are strongly recommended for patients with knee OA and conditionally recommended for patients with hand OA.

In keeping with the principle that medications with the least systemic exposure (i.e., local therapy) are preferable, topical NSAIDs should be considered prior to use of oral NSAIDs (24). Practical considerations (e.g., frequent hand washing) and the lack of direct evidence of efficacy in the hand lead to a conditional recommendation for use of topical NSAIDs in hand OA. In hip OA, the depth of the joint beneath the skin surface suggests that topical NSAIDs are unlikely to

Table 2. Recommendations for the pharmacologic management of osteoarthritis of the hand, knee, and hip

Intervention	Joint		
	Hand	Knee	Hip
Topical nonsteroidal antiinflammatory drugs			
Topical capsaicin			
Oral nonsteroidal antiinflammatory drugs			
Intraarticular glucocorticoid injection			
Ultrasound-guided intraarticular glucocorticoid injection			
Intraarticular glucocorticoid injection compared to other injections			
Acetaminophen			
Duloxetine			
Tramadol			
Non-tramadol opioids			
Colchicine			
Fish oil			
Vitamin D			
Bisphosphonates			
Glucosamine			
Chondroitin sulfate			
Hydroxychloroquine			
Methotrexate			
Intraarticular hyaluronic acid injection	(First carpometacarpal)		
Intraarticular botulinum toxin			
Prolotherapy			
Platelet-rich plasma			
Stem cell injection			
Biologics (tumor necrosis factor inhibitors, interleukin-1 receptor antagonists)			

Strongly recommended
Conditionally recommended
Strongly recommended against
Conditionally recommended against
No recommendation

confer benefit, and thus, the Voting Panel did not examine use in hip OA.

Topical capsaicin is conditionally recommended for patients with knee OA and conditionally recommended *against* in patients with hand OA.

Topical capsaicin is conditionally recommended for treatment of knee OA due to small effect sizes and wide confidence intervals in the available literature. We conditionally recommend against the use of topical capsaicin in hand OA because of a lack of direct evidence to support use, as well as a potentially increased risk of contamination of the eye with use of topical capsaicin to treat hand OA. In hip OA, the depth of the joint beneath the skin surface suggests that topical capsaicin is unlikely to have a meaningful effect, and thus, the Voting Panel did not examine use of topical capsaicin in hip OA. Insufficient data exists to make recommendations about the use of topical lidocaine preparations in OA.

Oral NSAIDs are strongly recommended for patients with knee, hip, and/or hand OA.

Oral NSAIDs remain the mainstay of the pharmacologic management of OA, and their use is strongly recommended. A large number of trials have established their short-term efficacy. Oral NSAIDs are the initial oral medication of choice in the treatment of OA, regardless of anatomic location, and are recommended over all other available oral medications.

While this guideline did not address the relative merits of different NSAIDs, there is evidence suggesting that certain agents may have more favorable side effect profiles than others (25–27). Clinical considerations aimed at risk mitigation for the safe use of NSAIDs, such as appropriate patient selection, regular monitoring for the development of potential adverse gastrointestinal, cardiovascular, and renal side effects and potential drug interactions, were not specifically included in the GRADE process for the formulation of recommendations. Doses should be as low as possible, and NSAID treatment should be continued for as short a time as possible.

Intraarticular glucocorticoid injections are strongly recommended for patients with knee and/or hip OA and conditionally recommended for patients with hand OA.

Trials of intraarticular glucocorticoid injections have demonstrated short-term efficacy in knee OA. Intraarticular glucocorticoid injection is conditionally, rather than strongly, recommended for hand OA given the lack of evidence specific to this anatomic location. There are insufficient data to judge the choice of short-acting over long-acting preparations or the use of low rather than high doses. A recent report (28) raised the possibility that specific steroid preparations or a certain frequency of steroid injections may contribute to cartilage loss, but the Voting Panel was uncertain of the clinical significance of this finding, particularly since

change in cartilage thickness was not associated with a worsening in pain, functioning, or other radiographic features.

Ultrasound guidance for intraarticular glucocorticoid injection is strongly recommended for injection into hip joints.

When available, ultrasound guidance for steroid injection may help ensure accurate drug delivery into the joint, but is not required for knee and hand joints. However, imaging guidance for injection into hip joints is strongly recommended.

Intraarticular glucocorticoid injections versus other injections are conditionally recommended for patients with knee, hip, and/or hand OA.

In OA generally, intraarticular glucocorticoid injection is conditionally recommended over other forms of intraarticular injection, including hyaluronic acid preparations. Head-to-head comparisons are few, but the evidence for efficacy of glucocorticoid injections is of considerably higher quality than that for other agents.

Acetaminophen is conditionally recommended for patients with knee, hip, and/or hand OA.

In clinical trials, the effect sizes for acetaminophen are very small, suggesting that few of those treated experience important benefit, and meta-analysis has suggested that use of acetaminophen as monotherapy may be ineffective (29). Longer-term treatment is no better than treatment with placebo for most individuals. Members of the Patient Panel noted that, for most individuals, acetaminophen is ineffective. For those with limited pharmacologic options due to intolerance of or contraindications to the use of NSAIDs, acetaminophen may be appropriate for short-term and episodic use. Regular monitoring for hepatotoxicity is required for patients who receive acetaminophen on a regular basis, particularly at the recommended maximum dosage of 3 gm daily in divided doses.

Duloxetine is conditionally recommended for patients with knee, hip, and/or hand OA.

While studied primarily in the knee, the effects of duloxetine may plausibly be expected to be similar for OA of the hip or hand. While a variety of centrally acting agents (e.g., pregabalin, gabapentin, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants) have been used in the management of chronic pain, only duloxetine has adequate evidence on which to base recommendations for use in OA. However, in considering all the ways in which OA may be affecting an individual patient, shared decision-making between the physician and patient may include consideration of any of these agents. Considering the utility of these agents in pain management generally, their use may be an appropriate target of future investigations specific to OA. Evidence suggests that duloxetine has efficacy in the treatment of OA when used alone or in combination with NSAIDs; however, there are issues regarding tolerability and side effects. No recommendations were made for the other centrally acting agents due to lack of direct studies of relevance in OA.

Tramadol is conditionally recommended for patients with knee, hip, and/or OA.

Recent work has highlighted the very modest level of beneficial effects in the long-term (3 months to 1 year) management of non-cancer pain with opioids (30). Nonetheless, there are circumstances in which tramadol or other opioids may be appropriate in the treatment of OA, including when patients may have contraindications to NSAIDs, find other therapies ineffective, or have no available surgical options. Patient Panel input demonstrated a high level of understanding concerning addiction potential, but also included an appreciation for the role of these agents when other pharmacologic and physical options have been ineffective. However, RCT evidence addressing the use of tramadol and other opioids for periods longer than 1 year is not available. Clinical trials have demonstrated some symptomatic efficacy, though concerns regarding potential adverse effects remain. If an opioid is being considered, tramadol is conditionally recommended over non-tramadol opioids.

Non-tramadol opioids are conditionally recommended *against* in patients with knee, hand, and/or hip OA with the recognition that they may be used under certain circumstances, particularly when alternatives have been exhausted.

As noted above, evidence suggests very modest benefits of long-term opioid therapy and a high risk of toxicity and dependence. Use of the lowest possible doses for the shortest possible length of time is prudent, particularly since a recent systematic review and meta-analysis suggests that less pain relief occurs during longer trials in the treatment of non-cancer chronic pain (30).

Colchicine is conditionally recommended *against* in patients with knee, hip, and/or hand OA.

Two very small studies have suggested analgesic benefit of colchicine in OA, but the quality of the data was low. In addition, potential adverse effects, as well as drug interactions, may occur with use of colchicine.

Fish oil is conditionally recommended *against* in patients with knee, hip, and/or hand OA.

Fish oil is the most commonly used dietary supplement in the US (31). Despite its popularity, only 1 published trial has addressed its potential role in OA. This study failed to show efficacy of a higher dose of fish oil over a lower dose.

Vitamin D is conditionally recommended *against* in patients with knee, hip, and/or hand OA.

A number of trials in OA demonstrated small effect sizes with vitamin D treatment, while others have shown no benefit and pooling data across studies yielded null results. In addition, limited

and questionable health benefits from vitamin D supplementation have been suggested in other contexts (32,33).

Bisphosphonates are strongly recommended *against* in patients with knee, hip, and/or hand OA.

Though a single small study of an oral bisphosphonate suggested a potential analgesic benefit in OA, the preponderance of data shows no improvement in pain or functional outcomes.

Glucosamine is strongly recommended *against* in patients with knee, hip, and/or hand OA.

Pharmaceutical-grade preparations of glucosamine are available and have been studied in multiple trials. However, discrepancies in efficacy reported in studies that were industry sponsored as opposed to publicly funded have raised serious concerns about publication bias (34,35). In addition, there is a lack of a clear biologic understanding of how efficacy would vary with the type of salt studied. The data that were deemed to have the lowest risk of bias fail to show any important benefits over placebo. These recommendations represent a change from the prior conditional recommendation against the use of glucosamine. The weight of the evidence indicates a lack of efficacy and large placebo effects. Nonetheless, glucosamine remains among the most commonly used dietary supplements in the US (31), and clinicians should be aware that many patients perceive that glucosamine is efficacious. Patients also often perceive that different glucosamine formulas are associated with different degrees of efficacy and seek advice on brands and manufacturers. The potential toxicity of glucosamine is low, though some patients exposed to glucosamine may show elevations in serum glucose levels (36).

Chondroitin sulfate is strongly recommended *against* in patients with knee and/or hip OA as are combination products that include glucosamine and chondroitin sulfate, but is conditionally recommended for patients with hand OA.

A single trial suggested analgesic efficacy of chondroitin sulfate, without evidence of harm, in hand OA.

Hydroxychloroquine is strongly recommended *against* in patients with knee, hip, and/or hand OA.

Well-designed RCTs of hydroxychloroquine, conducted in the subset of patients with erosive hand OA, have demonstrated no efficacy.

Methotrexate is strongly recommended *against* in patients with knee, hip, and/or hand OA.

Well-designed RCTs of methotrexate, conducted in the subset of patients with erosive hand OA, have demonstrated no efficacy.

Intraarticular hyaluronic acid injections are conditionally recommended *against* in patients with knee and/or first CMC joint OA and strongly recommended *against* in patients with hip OA.

In prior systematic reviews, apparent benefits of hyaluronic acid injections in OA have been reported. These reviews have not, however, taken into account the risk of bias of the individual primary studies. Our review showed that benefit was restricted to the studies with higher risk of bias: when limited to trials with low risk of bias, meta-analysis has shown that the effect size of hyaluronic acid injections compared to saline injections approaches zero (37). The finding that best evidence fails to establish a benefit, and that harm may be associated with these injections, motivated the recommendation against use of this treatment.

Many providers want the option of using hyaluronic acid injections when glucocorticoid injections or other interventions fail to adequately control local joint symptoms. In clinical practice, the choice to use hyaluronic acid injections in the knee OA patient who has had an inadequate response to nonpharmacologic therapies, topical and oral NSAIDs, and intraarticular steroids may be viewed more favorably than offering no intervention, particularly given the impact of the contextual effects of intraarticular hyaluronic acid injections (38). The conditional recommendation against is consistent with the use of hyaluronic acid injections, in the context of shared decision-making that recognizes the limited evidence of benefit of this treatment, when other alternatives have been exhausted or failed to provide satisfactory benefit. The conditional recommendation against is not intended to influence insurance coverage decisions.

In contrast, the evidence of lack of benefit is of higher quality with respect to hyaluronic acid injection in the hip. We therefore strongly recommend against hyaluronic acid injections in hip OA.

Intraarticular botulinum toxin injections are conditionally recommended *against* in patients with knee and/or hip OA.

The small number of trials of intraarticular botulinum toxin treatment in knee or hip OA suggest a lack of efficacy. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Prolotherapy is conditionally recommended *against* in patients with knee and/or hip OA.

A limited number of trials involving a small number of participants have shown small effect sizes of prolotherapy in knee or hip OA. However, injection schedules, injection sites, and comparators have varied substantially between trials. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Platelet-rich plasma treatment is strongly recommended *against* in patients with knee and/or hip OA.

In contrast to intraarticular therapies discussed above, there is concern regarding the heterogeneity and lack of standardization in available preparations of platelet-rich plasma, as well as techniques used, making it difficult to identify exactly what is being injected. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Stem cell injections are strongly recommended *against* in patients with knee and/or hip OA.

There is concern regarding the heterogeneity and lack of standardization in available preparations of stem cell injections, as well as techniques used. This treatment has not been evaluated in hand OA and, therefore, no recommendation is made with regard to OA of the hand.

Tumor necrosis factor inhibitors and interleukin-1 receptor antagonists are strongly recommended *against* in patients with knee, hip, and/or hand OA.

Tumor necrosis factor inhibitors and interleukin-1 receptor antagonists have been studied in trials using both subcutaneous and intraarticular routes of administration. Efficacy has not been demonstrated, including in erosive hand OA. Therefore, given their known risks of toxicity, we strongly recommended against their use for any form of OA.

Initial observations addressing the use of anti–nerve growth factor (anti-NGF) agents suggest that significant analgesic benefits may occur but that incompletely explained important safety issues may arise. A small subset of patients treated with these agents had rapid joint destruction leading to early joint replacement. The FDA temporarily halted clinical trials of anti-NGF as a result, but trials have since resumed, with ongoing collection of longer-term efficacy and safety data. As none of these agents were approved for use by the FDA and the longer-term data were not available at the time of the literature review and Voting Panel meeting, we are unable to make recommendations regarding the use of anti-NGF therapy.

DISCUSSION

These 2019 ACR/AF recommendations for the management of OA are based on the best available evidence of benefit, safety, and tolerability of physical, educational, behavioral, psychosocial, mind-body, and pharmacologic interventions, as well as the consensus judgment of clinical experts. The GRADE approach used provided a comprehensive, explicit, and transparent methodology for developing recommendations for OA management. The choice of any single or group of interventions may vary over the course of the disease or with patient and provider preferences, and is optimally arrived at through shared decision-making.

The Voting Panel made strong recommendations for patients to participate in a regular, ongoing exercise program. The literature provides support for choice from a broad menu of exercises for patients with OA. The effectiveness of an exercise program is enhanced when patient preferences and access to exercise programs are considered, as well as when they are supervised or coupled with self-efficacy, self-management, and weight loss programs. Strong recommendations were also made for weight loss in patients with knee and/or hip OA who are overweight or obese, self-efficacy and self-management programs, tai chi, cane use, first CMC joint orthoses, tibiofemoral bracing, topical NSAIDs for knee OA and oral NSAIDs for hand, knee, and/or hip OA, and intraarticular glucocorticoid injections for knee and/or hip OA. The Voting Panel made conditional recommendations for balance exercises, yoga, CBT, kinesiotaping, orthoses for hand joints other than the first CMC, patellofemoral bracing, acupuncture, thermal modalities, radiofrequency ablation, topical NSAIDs, intraarticular steroid injections and chondroitin sulfate for hand OA, topical capsaicin for knee OA, acetaminophen, duloxetine, and tramadol. The recommendations provide an array of options for a comprehensive approach for optimal management of OA encompassing the use of educational, physical, behavioral, psychosocial, mind-body, and pharmacologic interventions. The availability, accessibility, and affordability of some of these interventions vary, but in many communities the AF, as well as local hospitals and other health-related agencies, offer free self-efficacy and self-management programs.

For some patients with more limited disease in whom medication is required, topical NSAIDs represent an appropriate first choice. For others, particularly with hip OA or polyarticular involvement, oral NSAIDs are more appropriate. The appropriate use of other oral agents, particularly acetaminophen and opioids, will continue to evolve (39–41).

Despite the many options available, some patients may continue to experience inadequate symptom control; others will experience adverse effects from the available interventions. Clinicians treating patients in these circumstances should choose interventions with a low risk of harm, but both clinicians and patients may be dissatisfied with the options and unsure of how to choose among them. There are controversies in interpretation of the evidence, particularly with regard to the use of glucosamine and chondroitin, acupuncture, and intraarticular hyaluronic acid injections. Nonetheless, the process of updating treatment guidelines permits scrutiny of the state of the literature and identification of critical gaps in our knowledge about best practices. Further, it highlights the need for ongoing, appropriately funded, high-quality clinical research, as well as development of new treatment modalities, to address the human and economic impact of the most common form of arthritis.

No effective disease-modifying agents for OA have yet been identified though phase 2 and 3 trials are underway, and, for the time being, preventive strategies focus on weight management and injury prevention. Development of more effective therapies that

permit a sophisticated and individualized approach to the patient with OA await the outcome of future investigation. Important directions for research include gaining a more comprehensive understanding of the optimal types of exercises and the modifications that should be used based on disease location and severity, study of the intensity of exercise that would be optimal for a given individual (https://health.gov/paguidelines/second-edition/report.aspx), defining optimal footwear for patients with knee and hip OA and understanding the interaction between footwear and exercise, conducting rigorous RCTs for physical modality options in hand OA, assessing a broader array of outcomes, including fall prevention, assessing optimal use of oral, topical, and injectable agents alone and in combination, obtaining a better understanding of the role of integrative medicine, including massage, herbal products, medical marijuana, and additional mind-body interventions, and exploring agents with novel mechanisms of action for prevention and treatment.

In conclusion, optimal management requires a comprehensive, multimodal approach to treating patients with hand, hip, and/or knee OA offered in the context of shared decision-making with patients, to choose the safest and most effective treatment possible. A large research agenda remains to be addressed, with a need for more options with greater efficacy for the millions of people worldwide with osteoarthritis.

Addendum. Therapies that were approved after the original systematic literature review are not included in these recommendations.

ACKNOWLEDGMENTS

We thank Nancy Baker, ScD, MPH, OTR/l, Yvonne Golightly, PT, MS, PhD, Thomas Schnitzer, MD, PhD, and ChenChen Wang, MD, MSc for serving (along with authors Joel Block, MD, Leigh Callahan, PhD, Carole Dodge, OT, CHT, David Felson, MD, MPH, William F. Harvey, MD, MSc, Edward Herzig, MD, Marc C. Hochberg, MD, MPH, Sharon L. Kolasinski, MD, C. Kent Kwoh, MD, Amanda E. Nelson, MD, Tuhina Neogi, MD, PhD, Carol Oatis, PT, PhD, Jonathan Samuels, MD, Daniel White, PT, ScD, and Barton Wise, MD, PhD) on the Expert Panel. We thank Suzanne Schrandt, Angie Botto-van Bemden, and Jaffe Marie with the Arthritis Foundation for their involvement throughout the guideline development process. We thank the patients who (along with author Kathleen Gellar) participated in the Patient Panel meeting: Cindy Copenhaver, LMT, Donna Dernier, Fletcher Johnson, Nancy J. Maier, Travis Salmon, Elise Sargent, and Linda Walls. We thank the ACR staff, including Regina Parker for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project and Robin Lane for assistance in manuscript preparation. We thank Janet Waters for help in developing the literature search strategy and performing the literature search and updates, and Janet Joyce for peer-reviewing the literature search strategy.

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Arthritis Care & Research
Vol. 64, No. 4, April 2012, pp 465–474
DOI 10.1002/acr.21596
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SPECIAL ARTICLE

American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.

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Objective. **To update the American College of Rheumatology (ACR) 2000 recommendations for hip and knee osteoarthritis (OA) and develop new recommendations for hand OA.**

Methods. **A list of pharmacologic and nonpharmacologic modalities commonly used to manage knee, hip, and hand OA as well as clinical scenarios representing patients with symptomatic hand, hip, and knee OA were generated. Systematic evidence-based literature reviews were conducted by a working group at the Institute of Population Health, University of Ottawa, and updated by ACR staff to include additions to bibliographic databases through December 31, 2010. The Grading of Recommendations Assessment, Development and Evaluation approach, a formal process to rate scientific evidence and to develop recommendations that are as evidence based as possible, was used by a Technical Expert Panel comprised of various stakeholders to formulate the recommendations for the use of nonpharmacologic and pharmacologic modalities for OA of the hand, hip, and knee.**

Results. **Both "strong" and "conditional" recommendations were made for OA management. Modalities conditionally recommended for the management of hand OA include instruction in joint protection techniques, provision of assistive devices, use of thermal modalities and trapeziometacarpal joint splints, and use of oral and topical nonsteroidal antiinflammatory drugs (NSAIDs), tramadol, and topical capsaicin. Nonpharmacologic modalities strongly recommended for the management of knee OA were aerobic, aquatic, and/or resistance exercises as well as weight loss for overweight patients. Nonpharmacologic modalities conditionally recommended for knee OA included medial wedge insoles for valgus knee OA, subtalar strapped lateral insoles for varus knee OA, medially directed patellar taping, manual therapy, walking aids, thermal agents, tai chi, self-management programs, and psychosocial interventions. Pharmacologic modalities conditionally recommended for the initial management of patients with knee OA included acetaminophen, oral and topical NSAIDs, tramadol, and intraarticular corticosteroid injections; intraarticular hyaluronate injections, duloxetine, and opioids were conditionally recommended in patients who had an inadequate response to initial therapy. Opioid analgesics were strongly recommended in patients who were either not willing to undergo or had contraindications for total joint arthroplasty after having failed medical therapy. Recommendations for hip OA were similar to those for the management of knee OA.**

Conclusion. **These recommendations are based on the consensus judgment of clinical experts from a wide range of disciplines, informed by available evidence, balancing the benefits and harms of both nonpharmacologic and pharmacologic modalities, and incorporating their preferences and values. It is hoped that these recommendations will be utilized by health care providers involved in the management of patients with OA.**

INTRODUCTION

Many patients with a clinical diagnosis of osteoarthritis (OA) are treated with a combination of nonpharmacologic and pharmacologic modalities (1). The American College of Rheumatology (ACR) last published recommendations for the management of hip and knee OA in 2000 (2), with

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an addendum posted on the ACR web site in February 2005 (3). Since 2000, other professional societies have published recommendations for the management of hand, hip, and knee OA, including those developed by the European League Against Rheumatism (EULAR) (4–6), the Osteoarthritis Research Society International (OARSI) (7), and the American Academy of Orthopaedic Surgeons (AAOS) (8).

Past ACR recommendations for the management of hip and knee OA were derived by a small group using an informal consensus approach following an extensive literature review. Since then, the methodology used to develop clinical practice guidelines has matured with the use of systematic literature reviews and the implementation of the Delphi method for development of consensus agreement on propositions (4–7) or the RAND/University of California, Los Angeles Appropriateness Method for determining when the use of certain therapeutic modalities is appropriate in a given clinical scenario (9). The current recommendations were developed using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach, a formal process to develop recommendations that are as evidence based as possible. The GRADE approach has been adopted by the World Health Organization, the Cochrane Collaboration, the Agency for Healthcare Research and Quality (AHRQ) (10–14), and numerous professional organizations including, among others, the American College of Physicians and, most recently, the ACR.

Since 2000, new therapies for OA and additional information on the safety and tolerability of existing therapies for OA have become available and, as noted above, the methodology for developing clinical practice guidelines has evolved. These factors combined to contribute to the decision of the ACR to revise and update recommendations for the management of OA of the hip and knee as well as create new recommendations for the management of OA of the hand. Applying these recommendations in clinical practice requires individualized assessment of the patient and consideration of the values and judgments of both the practitioner and the patient. The recommendations provided here are not intended to be used in a "cookbook" fashion, but rather to provide guidance based on clinical evidence and expert panel input. Unlike previous ACR recommendations for the management of OA, these recommendations do not recommend the sequence of subsequent interventions for those failing to have an adequate response to recommended initial therapies, as there are few, if any, high-quality studies that were designed to examine the benefit and safety of specific modalities under such assumptions. Although disseminated under the aegis of the ACR, we hope that these recommendations will have relevance to practitioners throughout the world. We specifically did not make recommendations regarding the use of pharmacologic agents that are not approved in the US and Canada, however, or regarding the use of surgical interventions, as this was beyond the scope of the charge to the committee.

Dr. Hochberg has received consultant fees (less than $10,000 each) from Abbott Laboratories, Amgen, AstraZeneca, Bayer Health Care, Bioiberica, Bristol-Myers Squibb, CombinatoRx, Covidien, Eli Lilly, Genentech, GlaxoSmithKline, Hoffman-La Roche, Merck, Merck Serono International, NicOx, Novartis, Pfizer, Pozen, Rand Corporation, Sanofi-Aventis, Smith & Nephew, Stryker Biotech, TransPharma Medical, and UCB, receives research support from the NIH, serves as a member/chair of the data safety monitoring boards for the National Eye Institute and Novartis, and serves on the medical advisory board for and owns stock in Theralogix. Dr. Altman has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Ferring, Rotta, Endo, Novartis, Lilly, and Smith & Nephew. Dr. Towheed has received speaking fees from and/or serves on the advisory board for Amgen, Novartis, Bristol-Myers Squibb, Hoffman-La Roche, and Schering (less than $10,000 each). Dr. Tugwell has received consultant fees (more than $10,000 each) from Abbott, Almirall, AstraZeneca, Aventis, Berlex, Biomatrix, Bristol-Myers Squibb, Caduceus Group, Centocor, Chelsea, Dimedix, Dimethaid, Eli Lilly, Glaxo-Welcome, GlaxoSmithKline, Hoechst Marion Roussel, Immunomedics, Innovus, Johnson & Johnson, Larvol, Lilly Research, Medicine Group, Medicus, Merck, Merck Frosst, Novartis, Novopharm, Ortho McNeil, Pennside, Pfizer, Roche, Sandoz, Scios, Searle, Teva Pharmaceuticals, UCB, and Wyeth Ayerst, and has received grant support from Aventis, Biomatrix, Cigna, Genzyme, IDRC, Merck, Novartis, Parke-Davis, Pfizer, Rhone-Poulenc, Sandoz, and Smithkline Beecham.

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Submitted for publication April 1, 2010; accepted in revised form December 23, 2011.

MATERIALS AND METHODS

Initial systematic literature review. Systematic literature searches were conducted by a working group at the University of Ottawa, which also organized the summary evidence profiles and supporting documents. Systematic literature searches were performed for more than 50 different nonpharmacologic and pharmacologic modalities that were previously identified by separate expert panels (4–7); note that tramadol was considered separately from opioid analgesics because the central analgesic effect of tramadol is thought to be mediated not only by a weak opioid receptor agonist effect but also through modulation of serotonin and norepinephrine levels. Literature searches were not performed for medications that are not commercially available in the US and Canada. The initial searches were conducted in Medline (1950–2009), Embase (1980–2009), and The Cochrane Library (issue 3, 2009) by applying database subject headings and relevant keywords (see Supplementary Appendix A for the search strategy employed for exercise, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Published search filters were modified and used to limit the search to specific high-quality study designs (15–17). The initial searches for pharmacologic modalities were conducted during the third and fourth quarters of 2008, while those for the nonpharmacologic modalities were conducted during the second and third quarters of 2009.

The goal of the literature search was to identify the most current systematic review(s) and meta-analysis(es) that would provide reliable estimates of benefits of the inter-

vention for the prespecified clinically relevant outcomes of pain and function as well as providing data on safety of the intervention; clinically relevant safety outcomes differed by type of intervention. If no systematic review or meta-analysis was available, the search results were screened for randomized controlled trials (RCTs). If more than 1 systematic review or RCT was identified for the modality and outcomes of interest, the quality of the systematic review or RCT was assessed in order to select the best-quality evidence. Observational studies on safety of interventions were included if there were no RCTs. Data from the Food and Drug Administration (FDA) Adverse Event Reporting System and unpublished data from product manufacturers or investigators were not solicited, as adequate denominator populations are often not available to allow the calculation of numbers needed to harm.

Forming the Technical Expert Panel (TEP) and developing clinical scenarios. While the initial literature review was being completed, a TEP was convened (members of the TEP are shown in Appendix A). The TEP included nationally recognized academic and practicing rheumatologists, primary care physicians, physiatrists, geriatricians, orthopedic surgeons, and occupational and physical therapists. The TEP was asked initially to develop a series of clinical scenarios representing patients with hand, hip, or knee OA who presented for management decisions. The scenarios included a base case of a patient with symptomatic hand, hip, or knee OA; clinical variations of the base case scenario depended on specific joint groups involved for hand OA and the lack of a satisfactory response and/or the presence of comorbidities for hip and knee OA. The scenarios were collated and then submitted to the ACR Board of Directors for review.

Recommendation development. Once the literature review was completed, the TEP was asked to evaluate the evidence and formulate recommendations for OA treatment in the situations outlined in the clinical scenarios. First, the TEP was provided with summaries of the best available evidence for all interventions, including evidence profiles for each intervention for the prespecified clinically important outcomes, which provided summary data on the benefits and safety of each modality. These summaries also included, for each modality examined, the percentage of patients who clinically improved in both control and treatment groups, estimated effect size, number needed to treat, number needed to harm, and a complete quality assessment of the evidence. In addition, the TEP received the final set of clinical scenarios; instructions on the use of the GRADE process (10–13); the ACR White Paper on the use of nonsteroidal antiinflammatory drugs (NSAIDs) (18); AHRQ reports on the use of nonopioid analgesics for OA (19) and treatment of primary and secondary knee OA (20); the EULAR recommendations for the management of OA of the hand, hip, and knee (4–6); the AAOS recommendations for the management of knee OA (8); the OARSI recommendations for the management of OA of the hip and knee (7); the American Heart Association Scientific Statement on the use of NSAIDs (21); and the American College of Cardiology Foundation consensus recommendations on reducing the risk of gastrointestinal (GI) adverse events in patients using antiplatelet and NSAID therapy (22). The TEP also considered drug-specific indications, contraindications, and warnings from product information labels from the US FDA.

Next, using a 5-point Likert scale, panelists were asked to use the evidence reports to make a recommendation for each pharmacologic modality as applied to each clinical scenario; nonpharmacologic modalities were evaluated for the base cases of hand, hip, and knee OA, as well as hand OA with involvement of the trapeziometacarpal joint. The scale provided to panelists included the following choices: strong recommendation to use, weak (or conditional) recommendation to use, no recommendation, weak (or conditional) recommendation not to use, and strong recommendation not to use. The strength of a recommendation reflects the quality of the evidence supporting the use of the modality as well as the extent to which one can be confident that desirable effects (i.e., benefits) of an intervention outweigh undesirable effects (i.e., harms). Strong recommendations mean that most informed patients would choose the recommended management and that clinicians can structure their interactions with patients accordingly. Conditional recommendations mean that the majority of informed patients would choose the recommended management but many would not, so clinicians must ensure that patients' care is in keeping with their values and preferences. Based on this initial TEP member feedback, an initial set of recommendations was drafted.

Initial voting was done privately with votes submitted electronically using Excel spreadsheets (Microsoft). The TEP met in person in December 2008 to complete the pharmacologic recommendations for hand, hip, and knee OA and the nonpharmacologic recommendations for hand OA. If consensus was not achieved with private voting, further discussion of the modality was conducted at the meeting with open voting and group discussion until consensus was achieved. Subsequently, the TEP met by conference call in September 2009 to complete the nonpharmacologic recommendations for hip and knee OA. Prior to the conference call, the TEP members were provided with summary data on the benefits and safety of each nonpharmacologic modality reviewed. Again, initial voting was done privately with votes submitted electronically using Excel spreadsheets. If consensus was not achieved with private voting, further discussion of the modality was conducted at the meeting with open voting and group discussion until consensus was achieved. Throughout the voting process, if one or more members of the TEP reported a conflict of interest concerning any specific modality, they were encouraged to recuse themselves from the discussion and voting on that modality.

The summary data from the systematic literature review that were provided to the TEP before its meetings are available as supplementary files in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658. These data include not only the citations for the most relevant systematic reviews and/or randomized clinical trials and how to interpret them (in the OA guideline development process document), but also the summary of findings tables indicating the efficacy and safety/tolerability of pharmacologic modalities for hip and knee OA, duloxetine, nonpharmacologic modalities

for hip and knee OA, and updated tai chi. In addition, the top-line citations for each treatment modality that were used for the development of the summary of findings tables are included in Supplementary Appendix B (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

The final set of recommendations was drafted after discussion of the evidence at each TEP meeting. Consensus was defined as 75% or more of the members of the TEP voting to either strongly or conditionally recommend using a modality, either strongly or conditionally recommend not using a modality, or choosing not to make a recommendation on the use of a modality (23). A strong recommendation for using a modality required high-quality evidence and evidence of a large gradient of difference between desirable and undesirable effects of the treatment (i.e., benefits compared to harms). A conditional recommendation for using a modality was based on absence of high-quality evidence and/or evidence of only a small gradient of difference between desirable and undesirable effects of the treatment. In addition, when there was more uncertainty and/or variability in the values and preferences of the TEP members for a specific modality, this more likely resulted in a conditional recommendation. The lack of data from appropriate RCTs resulted in either not making a recommendation or making a recommendation not to use a modality, depending on the harms of the modality in other conditions and/or the values and preferences of TEP members. The recommendations of the TEP focus on the initiation of treatments for OA of the hand, hip, and knee. Costs of care were not considered in formulating these recommendations.

Updating the literature review and finalizing the recommendations. The initial literature searches were updated during the first quarter of 2011 with a cutoff date of December 31, 2010 by the ACR staff using the identical methodology and search filters as in the original searches. The results of the updated literature search of pharmacologic agents were reviewed by physician members of the project's Steering Committee (RDA, MCH, TT, PT) to identify studies that might provide information on new treatments or new information on the efficacy or safety/tolerability of existing treatments. The results of the updated literature search for nonpharmacologic modalities were reviewed by the rheumatology health professionals who were members of a TEP to identify studies that might provide new information on the efficacy or safety/tolerability of existing modalities. Selected key articles that were used to generate the evidence profiles for each of the nonpharmacologic and pharmacologic modalities are listed in Supplementary Appendix B (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

In the second quarter of 2011, the TEP reviewed the information obtained from the updated literature search and voted electronically on the need for making any changes in the original recommendations as well as providing recommendations for any new therapeutic modalities. Conference calls were conducted in order to reach consensus, as necessary. These updated votes are included in the recommendations in this manuscript.

ACR peer review of recommendations. Following manuscript development, a draft was submitted to the ACR Guideline Subcommittee, ACR Quality of Care Committee, and ACR Board of Directors for their comments and votes in regard to approval. These comments were incorporated into the final recommendations to the extent possible.

RESULTS

Hand OA. *Base case.* An adult with symptomatic hand OA without cardiovascular comorbidities, current or past upper GI problems, or chronic kidney disease presents to her primary care provider for treatment. She has pain in several finger joints for several months. Over-the-counter (OTC) acetaminophen at dosages up to 3 gm/day was of minimal value. Radiographs revealed osteophytes at several distal and proximal interphalangeal joints with joint space narrowing but no erosions.

The evidence base for hand OA was developed in collaboration with one of the authors (TT); this report has subsequently been published in part (24). There were relatively few high-quality RCTs of interventions for hand OA published in the peer-reviewed literature. Therefore, there were no strong recommendations made by the TEP for this indication. There are, however, several conditional recommendations that are discussed in the following sections.

Nonpharmacologic modalities. The TEP conditionally recommends that all patients with hand OA should be evaluated by a health professional, either their primary care provider or an occupational or physical therapist, for their ability to perform activities of daily living and receive assistive devices as necessary, instruction in joint protection techniques, and the use of thermal agents for relief of pain and stiffness (Table 1). The TEP conditionally recommends that patients with OA involving the trapeziometacarpal joint should be provided with splints, as they may benefit from this device.

Pharmacologic modalities. The TEP conditionally recommends that patients with hand OA should be treated

Table 1. Nonpharmacologic recommendations for the management of hand OA*

We conditionally recommend that health professionals should do the following:
Evaluate the ability to perform activities of daily living (ADLs)
Instruct in joint protection techniques
Provide assistive devices, as needed, to help patients perform ADLs
Instruct in use of thermal modalities
Provide splints for patients with trapeziometacarpal joint OA

* No strong recommendations were made for the nonpharmacologic management of hand osteoarthritis (OA). The evidence supporting these interventions demonstrated only a small to moderate effect size (see supplementary bibliography for hand OA in Supplementary Appendix B, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Table 2. Pharmacologic recommendations for the initial management of hand OA*

We conditionally recommend that health professionals should use one or more of the following:
Topical capsaicin
Topical NSAIDs, including trolamine salicylate
Oral NSAIDs, including COX-2 selective inhibitors
Tramadol
We conditionally recommend that health professionals should not use the following:
Intraarticular therapies
Opioid analgesics
We conditionally recommend that persons age ≥75 years should use topical rather than oral NSAIDs. In persons age <75 years, the TEP expressed no preference for using topical rather than oral NSAIDs.

* No strong recommendations were made for the pharmacologic management of hand osteoarthritis (OA). For patients who have an inadequate response to initial pharmacologic management, please see the Results for alternative strategies. NSAIDs = nonsteroidal antiinflammatory drugs; COX-2 = cyclooxygenase 2; TEP = Technical Expert Panel.

with either topical or oral NSAIDs, topical capsaicin, or tramadol (Table 2). The TEP conditionally recommends that such patients not be treated with opioid analgesics or intraarticular therapies.

For patients with involvement of the trapeziometacarpal joint who request an intraarticular injection, the TEP conditionally recommends not using either intraarticular corticosteroids or hyaluronates and, furthermore, provided no recommendation on the choice between corticosteroids and hyaluronates, if a provider decides to give an injection. For patients with erosive and/or inflammatory interphalangeal OA, the TEP conditionally recommends not using either oral methotrexate or sulfasalazine and voted not to provide a recommendation either for or against the use of hydroxychloroquine. The recommendations not to use modalities were based largely on the absence of evidence from RCTs to support the benefits of use of these modalities and the potential for harm from these agents and/or procedures.

Knee OA. *Base case.* An adult with symptomatic knee OA without cardiovascular comorbidities, current or past upper GI problems, or chronic kidney disease presents to her primary care provider for treatment. She experiences pain in and/or around her knee(s) and has not had an adequate response to either intermittent dosing of OTC acetaminophen, OTC NSAIDs, or OTC nutritional supplements (e.g., chondroitin sulfate, glucosamine).

Nonpharmacologic modalities. The TEP strongly recommends that all patients with symptomatic knee OA be enrolled in an exercise program commensurate with their ability to perform these activities (25,26) (Table 3). The TEP expressed no preference for aquatic exercises as opposed to land-based exercises based on benefits or safety; the decision should be individualized and based on patient preferences and ability to perform exercises. For example, a patient who is aerobically deconditioned should initially participate in an aquatic exercise program in order to improve their aerobic capacity. Once this is accomplished, they can progress to a land-based program and choose, in conjunction with their health care provider, an aerobic conditioning or strengthening program or both. The TEP also strongly recommends that all patients with symptomatic knee OA who are overweight be counseled regarding weight loss (27).

The TEP conditionally recommends that patients with knee OA should 1) participate in self-management programs that may include psychosocial interventions, 2) use thermal agents and manual therapy in combination with exercise supervised by a physical therapist, 3) use medially directed patellar taping, 4) participate in tai chi programs, and 5) use walking aids, if necessary. Patients with lateral compartment OA are conditionally recommended to wear medially wedged insoles, while those with medial compartment OA are conditionally recommended to wear laterally wedged subtalar strapped insoles.

Pharmacologic modalities. For the base case failing to obtain adequate pain relief with intermittent dosing of OTC acetaminophen, OTC NSAIDs, and/or OTC nutritional supplements (e.g., chondroitin sulfate, glucosamine), the TEP conditionally recommends that health

Table 3. Nonpharmacologic recommendations for the management of knee OA

We strongly recommend that patients with knee OA should do the following:
Participate in cardiovascular (aerobic) and/or resistance land-based exercise
Participate in aquatic exercise
Lose weight (for persons who are overweight)
We conditionally recommend that patients with knee OA should do the following:
Participate in self-management programs
Receive manual therapy in combination with supervised exercise
Receive psychosocial interventions
Use medially directed patellar taping
Wear medially wedged insoles if they have lateral compartment OA
Wear laterally wedged subtalar strapped insoles if they have medial compartment OA
Be instructed in the use of thermal agents
Receive walking aids, as needed
Participate in tai chi programs
Be treated with traditional Chinese acupuncture*
Be instructed in the use of transcutaneous electrical stimulation*
We have no recommendations regarding the following:
Participation in balance exercises, either alone or in combination with strengthening exercises
Wearing laterally wedged insoles
Receiving manual therapy alone
Wearing knee braces
Using laterally directed patellar taping

* These modalities are conditionally recommended only when the patient with knee osteoarthritis (OA) has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure.

Table 4. Pharmacologic recommendations for the initial management of knee OA*

We conditionally recommend that patients with knee OA should use one of the following:
Acetaminophen
Oral NSAIDs
Topical NSAIDs
Tramadol
Intraarticular corticosteroid injections
We conditionally recommend that patients with knee OA should not use the following:
Chondroitin sulfate
Glucosamine
Topical capsaicin
We have no recommendations regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics

* No strong recommendations were made for the initial pharmacologic management of knee osteoarthritis (OA). For patients who have an inadequate response to initial pharmacologic management, please see the Results for alternative strategies. NSAIDs = nonsteroidal antiinflammatory drugs.

care providers can use acetaminophen, oral or topical NSAIDs, tramadol, or intraarticular corticosteroid injections (Table 4). The TEP conditionally recommends that health care providers do not use nutritional supplements (e.g., chondroitin sulfate, glucosamine) or topical capsaicin. If the health care provider chooses to initiate acetaminophen in the full dosage up to 4,000 mg/day, the patient should be counseled to avoid all other products that contain acetaminophen, including OTC cold remedies as well as combination products with opioid analgesics.

If the patient does not have a satisfactory clinical response to full-dose acetaminophen, then the TEP strongly recommends the use of oral or topical NSAIDs or intraarticular corticosteroid injections (18,19). Health care providers should not use oral NSAIDs in patients with contraindications to these agents and should be aware of the warnings and precautions associated with the use of these agents. Furthermore, for persons age ≥75 years, the TEP strongly recommends the use of topical rather than oral NSAIDs (28). In this scenario, the TEP conditionally recommends the use of tramadol, duloxetine, or intraarticular hyaluronan injections. If the patient has a history of a symptomatic or complicated upper GI ulcer but has not had an upper GI bleed in the past year and the practitioner chooses to use an oral NSAID, the TEP strongly recommends using either a cyclooxygenase 2 (COX-2) selective inhibitor or a nonselective NSAID in combination with a proton-pump inhibitor; there was no preference expressed between these choices (29). In the clinical scenario where the above patient has had an upper GI bleed within the past year and the practitioner still chooses to use an oral NSAID, the TEP strongly recommends using a COX-2 selective inhibitor in combination with a proton-pump inhibitor. Subsequent to the initial meeting of the TEP, Latimer and colleagues reported that the addition of a proton-pump inhibitor to either a nonselective or COX-2 selective NSAID is cost effective given the evolving evidence base for efficacy and reductions in price (30). Therefore, whenever an NSAID is used for the chronic management of patients with knee or hip OA, the practitioner should consider adding a proton-pump inhibitor to reduce the risk of development of symptomatic or complicated upper GI events.

In the clinical scenario where the patient with OA is taking low-dose aspirin (≤325 mg per day) for cardioprotection and the practitioner chooses to use an oral NSAID, the TEP strongly recommends using a nonselective NSAID other than ibuprofen in combination with a proton-pump inhibitor. This recommendation is based, in part, on the FDA warning that the concomitant use of ibuprofen and low-dose aspirin may render aspirin less effective when used for cardioprotection and stroke prevention because of a recognized pharmacodynamic interaction (31,32). Studies have not demonstrated this same type of pharmacodynamic interaction with diclofenac or celecoxib (33,34); nonetheless, the TEP strongly recommends that a COX-2 selective inhibitor should not be used in the above situation. No specific recommendation was made regarding other individual NSAIDs.

Based on good clinical practice, oral NSAIDs should not be used in patients with chronic kidney disease stage IV or V (estimated glomerular filtration rate below 30 cc/minute); the decision to use an oral NSAID in patients with chronic kidney disease stage III (estimated glomerular filtration rate between 30 and 59 cc/minute) should be made by the practitioner on an individual basis after consideration of the benefits and risks.

Finally, for patients with symptomatic knee OA who have not had an adequate response to both nonpharmacologic and pharmacologic modalities and are either unwilling to undergo or are not candidates for total joint arthroplasty, the TEP strongly recommends the use of opioid analgesics and conditionally recommends the use of duloxetine. The authors suggest that practitioners follow the recommendations of the American Pain Society/American Academy of Pain Medicine for the use of opioid analgesics in the management of their chronic noncancer pain (35). These recommendations provide guidance on 1) patient selection and risk stratification, 2) informed consent and opioid management plans, 3) initiation and titration of chronic opioid therapy, 4) monitoring of patients on chronic opioid therapy, including dose escalations, high-dose opioid therapy, opioid rotation, and indications for discontinuation of therapy, 5) prevention and management of opioid-related adverse effects, and 6) management of breakthrough pain.

Treatment with traditional Chinese acupuncture or instruction in the use of transcutaneous electrical stimulation are conditionally recommended only when the patient with knee OA has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure (Table 3).

Hip OA. *Base case.* An adult with symptomatic hip OA without cardiovascular comorbidities, current or past up-

per GI problems, or chronic kidney disease presents to her primary care provider for treatment. As few trials have been performed in patients with symptomatic hip OA, the TEP considered that patients with hip OA should be treated in a similar fashion to those with knee OA except for selected differences.

Nonpharmacologic modalities. The TEP strongly recommends that all patients with symptomatic hip OA be enrolled in an exercise program commensurate with their ability to perform these activities (Table 5). The TEP expressed no preference for aquatic exercises as opposed to land-based exercises based on benefits or safety; the decision should be individualized and based on patient preferences and the ability to perform exercises. The TEP strongly recommends that all patients with symptomatic hip OA who are overweight be counseled regarding weight loss.

The TEP conditionally recommends that patients with hip OA should 1) participate in self-management programs that may include psychosocial interventions, 2) use thermal agents and manual therapy in combination with exercise supervised by a physical therapist, and 3) use walking aids, if necessary. Interventions for which data are available only for knee OA and not hip OA were not considered for patients with only hip OA (e.g., insoles, patellar taping, acupuncture, transcutaneous electrical stimulation, tai chi).

Pharmacologic modalities. The approach to pharmacologic therapy for the patient with hip OA is similar to that for the patient with knee OA except that no recommendations were made for intraarticular hyaluronates, duloxetine, or topical NSAIDs because of the lack of data from RCTs on either benefit or safety at the time of the TEP meeting in December 2008 (Table 6). Again, opioid analgesics are strongly recommended only for patients with symptomatic hip OA who have not had an adequate response to both nonpharmacologic and pharmacologic modalities and are either unwilling to undergo or are not candidates for total joint arthroplasty.

Table 5. Nonpharmacologic recommendations for the management of hip osteoarthritis (OA)

We strongly recommend that patients with hip OA should do the following:
Participate in cardiovascular and/or resistance land-based exercise
Participate in aquatic exercise
Lose weight (for persons who are overweight)
We conditionally recommend that patients with hip OA should do the following:
Participate in self-management programs
Receive manual therapy in combination with supervised exercise
Receive psychosocial interventions
Be instructed in the use of thermal agents
Receive walking aids, as needed
We have no recommendations regarding the following:
Participation in balance exercises, either alone or in combination with strengthening exercises
Participation in tai chi
Receiving manual therapy alone

Table 6. Pharmacologic recommendations for the initial management of hip OA*

We conditionally recommend that patients with hip OA should use one of the following:
Acetaminophen
Oral NSAIDs
Tramadol
Intraarticular corticosteroid injections
We conditionally recommend that patients with hip OA should not use the following:
Chondroitin sulfate
Glucosamine
We have no recommendation regarding the use of the following:
Topical NSAIDs
Intraarticular hyaluronate injections
Duloxetine
Opioid analgesics

* No strong recommendations were made for the initial pharmacologic management of hip osteoarthritis (OA). For patients who have an inadequate response to initial pharmacologic management, please see the Results for alternative strategies. NSAIDs = nonsteroidal antiinflammatory drugs.

DISCUSSION

These ACR 2012 recommendations for the management of patients with hand, hip, and knee OA are based on the best available evidence of benefit and safety/tolerability of both nonpharmacologic and pharmacologic interventions as well as the consensus judgment of clinical experts from a wide range of disciplines balancing the benefits and harms of these treatments and incorporating their preferences and values. We used the GRADE approach, which provides a comprehensive, explicit, and transparent methodology for developing recommendations for the management of patients (10–14,23,36). We included modalities that had been reviewed by other groups of experts in their recommendations published during the last decade (4–7,37) as well as modalities that have been investigated since the publication of these recommendations. The TEP was provided with a series of documents including not only the results of literature reviews, which provided the best available evidence to support the benefit and safety of pharmacologic and nonpharmacologic modalities, but also published recommendations from other professional societies (see above) prior to their voting. In addition, the TEP received documentation and formal instruction on implementation of the methodology. Therefore, these recommendations represent evidence- and expert consensus–based recommendations that should serve as a guide to health care providers in their approach to the management of patients with symptomatic OA. It is hoped that they may also be useful for the development and/or modification of quality measures for OA (38,39). As new evidence continues to be developed, it is likely that these recommendations will need to be updated and/or revised; such revisions will be posted, as appropriate, on the ACR web site (http://www.rheumatology.org/).

The authors acknowledge that, while most of the recommendations will not be controversial, some may be met

with disagreement by health care practitioners. One example is that of conditionally recommending against the use of glucosamine and chondroitin sulfate for patients with knee OA. The TEP relied initially on the results of the Glucosamine/Chondroitin Arthritis Intervention Trial (40) and meta-analyses that demonstrated significant heterogeneity in effect size (41–43) coupled with the lack of availability of prescription-quality preparations evaluated and approved for the indication of OA by the FDA. This original decision was reaffirmed after reviewing the results of a more recent network meta-analysis that also failed to demonstrate clinically important efficacy for these agents (44).

There have been many developments in the scientific and clinical understanding of OA in the past decade since the publication of the 2000 revised ACR recommendations (45,46). One of these developments is the publication of recommendations for the management of OA by numerous professional societies. These 2012 ACR OA guidelines improve upon these other recommendations in several ways. First, they are based on evidence available through the end of 2010. Second, they include recommendations for the management of hand OA as well as knee and hip OA. Third, they were developed using a rigorous transparent guideline development methodology that has been increasingly used by guideline developers in recent years. Finally, participants included the broadest group of experts to date on an OA guideline development project, representing several disciplines of health care providers with an interest in OA management.

When comparing these ACR guidelines to recent EULAR and OARSI guidelines, all rely on consensus recommendations based on the evidence. The EULAR recommendations are based on commissioned systematic reviews of the literature on both nonpharmacologic and pharmacologic modalities for OA of the hand, hip, and knee. OARSI commissioned a systematic review of the literature that updated those conducted for EULAR for OA of the hip and knee. Herein, literature reviews were conducted to identify the best available systematic review(s) and meta-analysis(es) for each of the modalities and, if these were not available, then the best available RCTs were selected.

All of the groups used a form of expert panel to provide the consensus recommendations. For the recommendations on hip and knee OA, the EULAR panel consisted of only rheumatologists and orthopedic surgeons; for the hand OA recommendations, EULAR added a physiatrist and 2 allied health professionals. The OARSI panel included 2 primary care physicians in addition to rheumatologists and an orthopedic surgeon. The ACR is the only professional society to include primary care physicians, physiatrists, and geriatricians along with rheumatologists (both academic and private practice), an orthopedic surgeon, and both physical and occupational therapists. Furthermore, the TEP had both sex and ethnic representations from constituencies within the ACR as well as members from both the US and Canada.

Both EULAR and OARSI used modifications of the Delphi technique to generate lists of propositions. This process required members of the Steering and Guideline Development Committees to amalgamate and rewrite or reword individual propositions submitted by members of the individual expert committees in order to reach consensus. The current ACR recommendations were developed using the GRADE process, a comprehensive, explicit, and transparent methodology that does not include the use of propositions; rather, the TEP used the best available evidence for the benefits and safety of each modality to produce specific recommendations, either strong, conditional, or none, for the use of each modality relative to a specific clinical scenario. These ACR recommendations acknowledge the values and preferences of the panel members for the desirable and undesirable outcomes of each modality.

It is hoped that with appropriate dissemination, these revised ACR guidelines will be utilized by health care providers in the management of their patients with OA.

Addendum. Therapies that were approved after the literature reviews are not included in these recommendations.

ACKNOWLEDGMENTS

The authors would like to acknowledge Elizabeth Tanjong Ghogomum, Lara Maxwell, Tamara Rader, and Erin Ueffing from the University of Ottawa for their assistance with the Ottawa team in preparing documentation for the panel members, and Amy Miller from the ACR for her support during this process.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Hochberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hochberg, Altman, April, McGowan, Towheed, Welch, Wells, Tugwell.

Acquisition of data. Altman, April, Benkhalti, McGowan, Towheed, Welch, Wells, Tugwell.

Analysis and interpretation of data. Hochberg, Altman, April, Benkhalti, Guyatt, McGowan, Towheed, Welch, Wells, Tugwell.

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APPENDIX A: MEMBERS OF THE TECHNICAL EXPERT PANEL

Members of the Technical Expert Panel are as follows: Roy D. Altman, MD (Chair): David Geffen School of Medicine, University of California, Los Angeles; Catherine L. Backman, PhD, OT: University of British Columbia, Vancouver, British Columbia, Canada; Lee I. Blecher, MD: Virginia Commonwealth University School of Medicine, Richmond, and Private Practice, Fairfax, Virginia; G. Kelley Fitzgerald, PhD, PT, C. Kent Kwoh, MD: University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; F. Michael Gloth, MD: The Johns Hopkins University School of Medicine, Baltimore, Maryland; Victor Goldberg, MD: Case Western Reserve University School of Medicine, Cleveland, Ohio; William McCarberg, MD: Kaiser Permanente, San Diego, California; Stephanie McGann, MD: University of Maryland School of Medicine, Baltimore (current address: Private Practice, Laurel, Maryland); Carol A. Oatis, PhD, PT: Arcadia University, Glenside, Pennsylvania; Robert Pallay, MD: Private Practice, Savannah, Georgia; Thomas J. Schnitzer, MD, PhD: Rehabilitation Institute of Chicago and Northwestern University, Chicago, Illinois; Radames Sierra-Zorita, MD: Private Practice, San Juan, Puerto Rico; Todd Stitik, MD: University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark.

ACR OA Guidelines
Non-pharmacological - Knee and Hip
September 2009

Table of Contents

1. EXERCISE 4

1.1 Balance exercises 4
1.1.1 Home-based balance exercises versus home-based strengthening exercises for knee OA 4
1.1.2 Balance exercises in addition to strengthening exercises versus strengthening exercises alone for knee OA 8

1.2 Land-based exercise 12
1.2.1 Cardiovascular land-based exercise versus usual care for knee OA 12
1.2.2 Resistance land-based exercise versus usual care for knee OA 16

1.3 Aquatic exercises 19
1.3.1 Aquatic exercise versus no exercise for OA of hip or knee 19
1.3.2 Aquatic exercise versus land-based exercise of knee OA 23

1.4 Tai chi 27

1.5 General hip exercise 31

2. INSOLES 34

2.1 Laterally wedged insoles versus neutrally wedged insoles for knee OA 34

2.2 Medial wedged insoles versus neutrally wedged insoles for knee OA 37

2.3. Subtalar strapped insoles versus inserted laterally wedged insoles for knee OA 40

3. SELF-MANAGEMENT 45

4. MANUAL THERAPY 49

4.1 Manual therapy program versus exercise therapy program for hip OA 49

4.2 Manual therapy in combination with supervised exercise and home exercise program versus home exercise program alone for knee OA 56

5. PSYCHOSOCIAL INTERVENTIONS 60

6. WEIGHT LOSS 64

7. BRACES 67

7.1 Braces and medical (conservative) treatment versus medical (conservative) treatment in knee OA 67

7.2 Braces with medical (conservative) treatment versus medical (conservative) treatment alone in knee OA 71

7.3 Braces and medical treatment versus neoprene sleeve with medical treatment in knee OA..... 74

8. TAPING 78

8.1 Medially-directed patellar taping versus no taping in knee OA 78

8.2 Medially-directed patellar taping versus sham taping in knee OA..... 82

8.3 Laterally-directed patellar taping versus medially-directed patellar taping in knee OA..... 87

8.4 Laterally-directed patellar taping versus neutral sham taping in knee OA..... 91

ABBREVIATIONS..... 95

GRADE EVIDENCE PROFILES..... 96

Table 1 a: Home-based balance exercises versus home-based strengthening exercises for knee OA 96
Table 1 b: Balance exercises in addition to strengthening exercises versus strengthening exercises alone for knee OA 97
Table 1 c: Cardiovascular land-based exercise versus usual care for knee OA 98
Table 1 d: Resistance land-based exercise versus usual care for knee OA 99
Table 1 e: Aquatic exercise versus no exercise for OA of hip or knee 100
Table 1 f: Aquatic exercise versus land-based exercise for knee OA 101
Table 1 g: Tai Chi compared to no exercise (education on OA) for knee OA 102
Author(s): Jessie McGowan, Maria Benkhalti **Date:** 2009-07-23 **Question:** Should tai chi versus no exercise (education on OA) be used for osteoarthritis of the knee? **Settings: Bibliography:** 102
Table 1 h: Exercise compared to no exercise for osteoarthritis of the hip 103
Table 2 a: Laterally wedged insoles versus neutrally wedged insoles for knee OA 103
Table 2 b: Medial wedged insoles versus neutrally wedged insoles for knee OA 104
Table 2 c: Subtalar strapped insoles versus inserted laterally wedged insoles for knee OA..... 105

Table 3: Self-management programs for knee OA 106
Table 4 a: Manual therapy program versus exercise therapy program for hip OA 107
Table 4 b: Manual therapy in combination with supervised exercise and home exercise program versus home exercise program alone for knee OA 108
Table 5: Psychosocial intervention compared to no intervention for OA of the hip and knee 109
Table 6: Weight loss compared to control (no weight loss program) for knee OA 110
Table 7 a: Braces and medical (conservative) treatment versus medical (conservative) treatment knee OA 111
Table 7 b: Braces and medical (conservative) treatment versus medical (conservative) treatment alone in knee OA 112
Table 7 c: Braces and medical treatment versus neoprene sleeve with medical treatment in knee OA 113
Table 8 a: Medially-directed patellar taping versus no taping in knee OA 114
Table 8 b: Medially-directed patellar taping versus sham taping in knee OA 115
Table 8 c: Laterally-directed patellar taping versus medially-directed patellar taping in knee OA 116
Table 8 d: Laterally-directed patellar taping versus neutral sham taping in knee OA 117

1. EXERCISE

1.1 Balance exercises

1.1.1 Home-based balance exercises versus home-based strengthening exercises for knee OA

Are balance exercises effective in reducing pain and improving function in patients with symptomatic knee OA compared to strengthening exercises?

Step 1: Search Results

There were no SRs which reported the efficacy of balance exercises specifically in patients with OA (Orr, 2008, assessed the efficacy of progressive resistive training which is a different treatment and Howe, 2007 did not report any study with OA patients). There was one RCT which assessed the efficacy of balance exercises versus strengthening exercises in OA patients: Chaipinyo, 2009.

Intervention description: Participants in the balance group performed 30 repetitions of stepping forward and backward then sideways for each leg, 5 days a week for 4 weeks. They also performed 30 repetitions of a bilateral mini squat within pain free range (i.e., 15-30 degrees of knee flexion) in order to strengthen the quadriceps muscle in standing. The sequence of the exercises was as follows: stepping forward and backward with left leg 30 times, bilateral mini squat 10 times, stepping forward and backward with right leg 30 times, bilateral mini squat 10 times, stepping sideward to the left 30 times, bilateral mini squat 10 times, stepping sideward to the right 30 times. Exercises were performed at home.

Step 2: GRADE Summary of findings

*This study has a small sample size (n=42), which could undermine its validity.
*Participants in the strength group performed 30 repetitions of isometric knee extension in sitting for each leg, 5 days a week.

Home-based balance training compared to home-based strength training for knee OA

Patient or population: patients with knee OA
Intervention: home-based balance training
Comparison: home-based strength training

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **strength training**	Corresponding risk **Balance training**					
Benefits							
Pain Knee injury and Osteoarthritis Outcome Score (KOOS). Scale from: 0 to 100. Follow-up: 4 weeks	30%	22% (8% to 44%)[1]	-8%	0.73	42 (1 study)	⊕⊕OO low[2,3,4]	Not statistically significant *Balance training shows less improvement in pain than strength training.
function in daily living Knee injury and Osteoarthritis Outcome Score (KOOS). Scale from: 0 to 100. Follow-up: 4 weeks	28%	15% (5% to 34%)[1]	-13%	0.54	42 (1 study)	⊕⊕OO low[2,3,4]	Not statistically significant *Balance training shows less improvement in function than strength training.
Harms							
Adherence (average number of days of exercise performed by participants) Maximum number of days:28. Follow-up: 4 weeks	Mean (SD) 19 (3)	Mean (SD) 21 (6)	MD 2 (-0.77 to 4.77)	-	42 (1 study)	⊕⊕OO low[2,3,4]	Not statistically significant *Balance training shows better adherence than strength training.
Withdrawals (patients who withdrew from the study after randomization) Follow-up: 4 weeks	25%	2% (0% to 32%)[5]	-23%	0.08 (0.00 to 1.29)	48 (1 study)	⊕⊕OO low[2,3,4]	Not statistically significant *Balance training shows less withdrawals than strength training.
Safety				Not reported			

[1] The authors report the mean difference over time between groups but it does not coincide with our results using Rev Man 5 because the authors did not report the level of accuracy needed (no decimals reported). We calculated the SMD using Rev Man 5.
[2] The physiotherapists prescribing the exercises were not blinded to group allocation. We did not downgrade the quality assessment score for this. However, the number of patients in this trial is small (n=42), which could undermine its validity.
[3] Participants were volunteers from the community 50 years and older. We did not downgrade the quality assessment score for this.
[4] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[5] Withdrawals were due to other illnesses, personal reasons or impossibility to reach patients.

Visual Summary of findings figure:
Home-based balance training compared to home-based strength training for knee OA

Chance: Improving pain after 4 weeks	
NNT: n/a	**Not statistically significant**
😐 70 people out of 100 don't improve with either type of training.	
🙂 22 people out of 100 improve with either type of training.	
😐 **8 FEWER people** out of 100 improve with balance training at home.	
Chance: Improving function after 4 weeks	
NNT: n/a	**Not statistically significant**
😐 72 people out of 100 don't improve with either type of training.	
🙂 15 people out of 100 improve with either type of training.	
😐 **13 FEWER people** out of 100 improve with balance training at home.	
Chance: Adherence after 4 weeks	
NNH: n/a	**Not statistically significant**
😐 On average, people performed the exercises for 19 days with either type of training	
☹ On average, people did not perform the exercises for 7 days (out of maximum possible of 28 days) with either type of training	
☹ On average, people performed exercises for **2 less** days with strengthening than balance training at home.	
Chance: Withrawals from the trials after 4 weeks	
NNH: n/a	**Not statistically significant**
😐 75 people out of 100 did not drop out of either type of training.	
☹ 2 people out of 100 dropped out of either type of training..	
🙂 **23 fewer people** out of 100 dropped out of balance training at home.	

Step 3: GRADE Evidence profile
See Table 1 a: Home-based balance exercises versus home-based strengthening exercises

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	We recommend patients with symptomatic OA of the knee be encouraged to participate in low-impact aerobic fitness exercises. Range of motion/flexibility exercises are an option for patients with symptomatic OA of the knee. We suggest quadriceps strengthening for patients with symptomatic OA of the knee.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, *insoles*, knee bracing) and weight reduction.
OARSI	Patients with hip and knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle strengthening and range of motion exercises.

Step 5: GRADE Recommendation

References

Chaipinyo K, Karoonsupcharoen O. No difference between home-based strength training and home-based balance training on pain in patients with knee osteoarthritis: a randomised trial. Aust J Physiother 2009;55(1):25-30.

1.1.2 Balance exercises in addition to strengthening exercises versus strengthening exercises alone for knee OA

Are balance exercises in addition to strengthening exercises effective in reducing pain and improving function in patients with symptomatic OA compared to strengthening exercises alone?

Step 1: Search Results

There were no SRs which reported the efficacy of balance exercises specifically in patients with OA (Orr, 2008 assessed the efficacy of progressive resistive training which is a different treatment and Howe, 2007 did not report any study with OA patients). There was one RCT which assessed the efficacy of balance exercises in addition to strengthening exercises vs. strengthening exercises alone (Diracoglu, 2005).

Intervention description: The first group (kinesthesia group) received kinesthesia, balance, and strengthening exercises and the second group (strengthening group) received only strengthening exercises. Patients in both groups were informed about knee OA and protective recommendations for the knee were made. The exercises were done 3 days a week in groups of 5 people in a clinical setting under the supervision of a physiotherapist. The total duration of the exercises was determined as 8 weeks. Isometric exercises were applied with 6-second contractions with 8 repetitions and a rest period of 2 seconds. Isotonic exercises were started from the third week and the maximum weight that can be lifted 10 times (10-repetition maximum = 10 RM) was determined. The exercises were applied as 10 repetitions with half of this weight, 10 repetitions with three fourths of this weight, and 10 repetitions with the whole 10 RM.10 RM was determined again every week.

Step 2: GRADE Summary of findings

kinesthesia and balance exercises in addition to strengthening exercises compared to strengthening exercises for knee OA

Patient or population: patients with knee OA
Intervention: kinesthesia and balance exercises in addition to strengthening exercises
Comparison: strengthening exercises

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk	Corresponding risk					
	strengthening exercises	kinesthesia and balance exercises in addition to strengthening exercises					
Benefits							

Physical function WOMAC. Scale from: 0 to 10. Follow-up: 8 weeks	31%	48% (29% to 68%)[1]	17%	1.55	60 (1 study)	⊕⊕OO low[2,3,4]	Not statistically significant
Pain	No evidence available[5]						
Harms							
Adverse effects number of patients with event Follow-up: 8 weeks	0%	0%	0%	1	60 (1 study)	⊕⊕⊕O moderate[2,3]	Not statistically significant
Adherence mean number of missed visits Maximum number of visits:24 Follow-up: 8 weeks	Mean 6	Mean 4	MD -2	-	48 (1 study)	⊕⊕⊕O moderate[2,3]	Not statistically significant
Withdrawals number of patients who withdrew after randomization Follow-up: 8 weeks	9%	9% (2% to 42%)[6]	0%	1 (0.22 to 4.6)	66 (1 study)	⊕⊕⊕O moderate[2,3]	Not statistically significant

[1] The authors reported the end of study results in both groups, which showed a statistically significant difference. However, their results did not coincide with our results from Rev Man 5 because the authors did not report the level of accuracy needed.
[2] The randomization method used is the "one-to-one" method which allocates one patient to the study group and the other patient to the control group one by one according to their order of application to the outpatient clinic. This method could lead to biases. Furthermore, blinding was not reported and intention to treat analyses were not performed.
[3] All patients included in the study were women 35 to 65 years old. We did not downgrade the quality of the study because of this.
[4] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[5] Pain was not measured in the RCT. However, the use of paracetamol was reported, which could represent a proxy measure for pain to some extent. The authors report that 5 patients used paracetamol during the study in a dosage of less than 500 mg daily. The 2 groups were not significantly different from each other regarding paracetamol use ($P > 0.05$).
[6] Patients withdrew because of the difficulty to come to the clinic for exercises.

Visual Summary of findings figure:
Kinesthesia and balance exercises in addition to strengthening exercises compared to strengthening exercises for knee OA

<table>
<tr><td colspan="2">Chance: Improving function after 8 weeks</td></tr>
<tr><td colspan="2">NNT: n/a</td><td rowspan="4">Not statistically significant</td></tr>
<tr><td>😐</td><td>52 people out of 100 don’t improve with either type of training.</td></tr>
<tr><td>☺</td><td>31 people out of 100 improve with either type of training.</td></tr>
<tr><td>☺</td><td>17 more people out of 100 improve with kinesthesia and balance exercises in addition to strengthening exercises.</td></tr>
<tr><td colspan="2">Chance: Improving pain after 8 weeks</td></tr>
<tr><td colspan="2">NNT: n/a</td><td></td></tr>
<tr><td colspan="3">Pain was not measured in this study, but there may be no difference in pain. People used the same amount of paracetomol (a pain reliever) whether they did kinesthesia and balance exercises in addition to strengthening exercises or just strengthening exercises</td></tr>
<tr><td colspan="2">Chance: Adverse events after 8 weeks</td></tr>
<tr><td colspan="2">NNH: n/a</td><td rowspan="2">Not statistically significant</td></tr>
<tr><td colspan="2">0 People out of 100 experienced adverse events.</td></tr>
<tr><td colspan="2">Chance: Adherence after 8 weeks</td></tr>
<tr><td colspan="2">NNH: n/a</td><td rowspan="3">Not statistically significant</td></tr>
<tr><td>😐</td><td>On average, people attended 18 visits with either type of training</td></tr>
<tr><td>☹</td><td>On average, people missed 4 visits with either type of training (out of maximum possible of 24 visits)</td></tr>
<tr><td colspan="2">Chance: Withdrawals from the trials after 8 weeks</td></tr>
<tr><td colspan="2">NNH: n/a</td><td rowspan="2">Not statistically significant</td></tr>
<tr><td>😐</td><td>91 people out of 100 did not drop out of either type of exercise.</td></tr>
</table>

☹	9 people out of 100 dropped out of either type of exercise.	
☹	**There was no difference in the number of people** out of 100 who dropped out of kinesthesia and balance exercises in addition to strengthening exercises.	

Step 3: GRADE Evidence profile
See Table 1b: Balance exercises in addition to strengthening exercises versus strengthening exercises alone

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	We recommend patients with symptomatic OA of the knee be encouraged to participate in low-impact aerobic fitness exercises. Range of motion/flexibility exercises are an option for patients with symptomatic OA of the knee. We suggest quadriceps strengthening for patients with symptomatic OA of the knee.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, *insoles*, knee bracing) and weight reduction.
OARSI	Patients with hip and knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle strengthening and range of motion exercises.

Step 5: GRADE Recommendation

References

Diracoglu D, Aydin R, Baskent A, Celik A. Effects of kinesthesia and balance exercises in knee osteoarthritis. J Clin Rheumatol 2005;11(6):303-10.

1.2 Land-based exercise

1.2.1 Cardiovascular land-based exercise versus usual care for knee OA

Is cardiovascular land exercise effective in reducing pain and improving function in patients with symptomatic knee osteoarthritis (OA) compared to usual care?

Step 1: Search Results

Three systematic reviews (SR) were found. Pisters (2007), was excluded from this comparison because it did not provide a description of the exercises used (combination of land, water, balance) and it did not report adherence. The second, Hart (2008), was excluded because it did not focus on osteoarthritis patients. Therefore, Fransen (2008) was chosen as the best available evidence. One overview of SRs on therapeutic exercise was found (Taylor, 2007) and its overall conclusions followed those of the chosen SR. Four randomized controlled trials published after the chosen SR were also found (Chua, 2008; Lund, 2008; Dincer, 2008; Olejarova, 2008). Their results were largely similar to those of the chosen SR. Evidence for withdrawals were extracted from the best RCT from Fransen, 2008: Ettinger, 1997.

Interventions description: non-perioperative walking program

Step 2: GRADE Summary of findings

	cardiovascular land exercise compared to no exercise for osteoarthritis of the knee						
	Patient or population: patients with osteoarthritis of the knee **Settings:** **Intervention:** cardiovascular land exercise **Comparison:** no exercise						
Outcomes	**Illustrative comparative risks* (95% CI)** Assumed risk **no exercise**	Corresponding risk **cardiovascular land exercise**	**Absolute difference**	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**NNT**
Benefits							
pain pooled studies with different scales including WOMAC and VAS amongst others	24%	41% of those cardiovascular exercise group experienced a decrease in pain (31% to 55%)	17%	1.71	351 (4[3])	⊕⊕⊕⊕ **high**[1]	5 (3 to 12)

function pooled studies with different scales including WOMAC and VAS amongst others	22%	34% of those cardiovascular exercise group experienced a decrease in pain (26% to 43%)	12%	1.55	317 (3[4])	⊕⊕⊕⊕ **high**[1]	7 (4 to 20)
Harms							
withdrawals number of (follow-up: mean 18 months)	**15%**	**19%** (11% to 31%)	**4%**	**RR 1.27** (0.76 to 2.12)	293 (1[5])	⊕⊕⊕O **moderate**	Not statistically significant
Safety (falls while walking)	1.4% of intervention group fell during walking (2/144)			**RR 5.17** (0.25 to 106.82)	293 (1[5])	⊕⊕⊕O **moderate**	Not statistically significant
Adherence	**95%**	**68%** (60% to 76%)	**27%**	**RR 0.71** (0.63 to 0.80)	293 (1[5])	⊕⊕⊕⊕ **high**	5 (4 to 7)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Evidence mostly included participants with early or mild symptomatic disease.
[3] Minor 1989, Ettinger 1997, Bautch 1997, Talbot 2003
[4] Minor 1989, Ettinger 1997, Bautch 1997
[5] Is imprecise; includes no effect and significant benefit (0.76, 2.12)
[6] Ettinger 1997

Visual Summary of Findings Table
Cardiovascular land exercise compared to no exercise for osteoarthritis of the knee

Chance: Improving pain

NNT: 5

59 people out of 100 don't improve whether or not they exercise.

24 people out of 100 improve whether or not they exercise.

17 more people out of 100 improve with cardiovascular land-based exercise.

Chance: Improving function

NNT: 7		
😐	66 people out of 100 don't improve whether or not they exercise.	
🙂	22 people out of 100 improve whether or not they exercise.	
🙂	**12 more people** out of 100 improve with land-based cardiovascular exercise	
Chance: Withdrawls after 18 months		
NNH: n/a		**Not statistically significant**
😐	85 people out of 100 did not leave the study whether they exercised or not.	
☹	9 people out of 100 left the study whether they exercised or not.	
☹	**4 more** people out of 100 left the study when they did land-based exercise.	
Chance: Safety		
1 person out 100 fell while walking		
Chance: Adherence*		
NNH: 5		
😐	68 people out of 100 adhered to either exercise or their normal activities	
☹	5 people out of 100 did not adhere to either exercise or their normal activities.	
☹	**27 more** people out of 100 did not adhere to the exercise.	

*does not add up to 100 due to rounding.

Step 3: GRADE Evidence profile

See Table 1 c: Cardiovascular land-based exercise versus usual care

Step 4: Other recommendations

Group	Recommendation
EULAR	Non-pharmacological treatment of knee OA should include education, *exercise*, appliances (sticks, insoles, knee bracing) and weight reduction.
OARSI	Patients with hip and knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle strengthening and range of motion exercises. For patients with systematic hip OA, exercises in the water can be effective.
AAOS (knee only)	We recommend patients with symptomatic OA of the knee be encouraged to participate in low-impact aerobic fitness exercises. Range of motion/flexibility exercises are an option for patients with symptomatic OA of the knee. We suggest quadriceps strengthening for patients with symptomatic OA of the knee.

Step 5: GRADE Recommendation

References

Bautch JC, Malone DG, Vailas AC. Effects of exercise on knee joints with osteoarthritis: a pilot study of biologic markers. Arthritis Care Res 1997;10(1):48-55.

Ettinger WH, Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). JAMA 1997;277(1):25-31.

Fransen M, McConnell S. Exercise for osteoarthritis of the knee. Cochrane Database of Syst Rev 2008;(4):CD004376.

Minor MA, Hewett JE, Webel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum 1989;32(11):1396-405.

Talbot LA, Gaines JM, Huynh TN, Metter EJ. A home-based pedometer-driven walking program to increase physical activity in older adults with osteoarthritis of the knee: a preliminary study. J Am Geriatr Soc 2003;51(3):387-92.

1.2.2 Resistance land-based exercise versus usual care for knee OA

Is resistance land exercise effective in reducing pain and improving function in patients with symptomatic knee OA compared to usual care?

Step 1: Search Results

Three systematic reviews (SR) were found. One, Pisters (2007), was excluded from this comparison because it did not provide a description of the exercises used (combination of land, water, balance) and it did not report adherence. The second, Hart (2008), was excluded because it did not focus on osteoarthritis patients. Therefore, Fransen (2008) was chosen as best available evidence. One overview of SR on therapeutic exercise was found (Taylor, 2007) and its overall conclusions followed those of the chosen SR. Four randomized controlled trials published after the chosen SR were also found (Chua, 2008; Lund, 2008; Dincer, 2008; Olejarova, 2008). Their results were largely similar to those of the chosen evidence. Safety, adherence, and withdrawals were not included in the best RCT included in Fransen, 2008 (Huang, 2005).

Intervention description: non-perioperative lower limb muscle strengthening

Step 2: GRADE Summary of findings

resistance land exercise compared to no exercise for knee OA

Patient or population: patients with osteoarthritis of the knee
Settings:
Intervention: resistance land exercise
Comparison: no exercise

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk	Corresponding risk					
	no exercise	**resistance land exercise**					
Benefits							
Pain pooled studies with different scales including WOMAC and VAS amongst others	32%	53% of those in strengthening exercise group experienced a decrease in pain (43% to 63%)	21%	1.66	1383 (9[3])	⊕⊕⊕O **moderate**[1,2]	4 (3 to 8)
Function pooled studies with different scales including	10%	25% of those in strengthening exercise group experienced a decrease in pain	15%	2.5	1383 (9[3])	⊕⊕⊕O **moderate**[1,2]	6 (4 to 22)

WOMAC and VAS amongst others		(35% to 69%)					
Harms							
Safety	14% patients in exercise group stopped due to intolerable pain during exercise.						
Adherence	Not reported						
Withdrawals	**9%**	**14%** (4 to 56%)	**5%**	**RR 1.67** (0.43 to 6.45)	70 (1[4])	⊕⊕⊕⊕ **high**	Not statistically significant

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Evidence mostly included participants with early or mild symptomatic disease.
[2] Large confidence interval ranging from small to large effect
[3] Schilke 2006, Ettinger 1997, Baker 2001, Thomas 2002, Gur 2002, Huang 2003, Huang 2005, Thorstensson 2005, Mikesky 2006
[4] Huang 2005

Visual Summary of Findings Table
Resistance land exercise compared to no exercise for osteoarthritis of the knee

Chance: Improving pain

NNT: 4

47 people out of 100 don't improve whether or not they exercise.

32 people out of 100 improve whether or not they exercise.

21 more people out of 100 improve with exercise.

Chance: Improving function

NNT: 6

75 people out of 100 don't improve whether or not they exercise.

☺	10 people out of 100 improve whether or not they exercise.	
☺	**15 more people** out of 100 improve with exercise	
Chance: Withdrawals		
NNH: n/a		**Not statistically significant**
😐	86 people out of 100 did not leave the study whether they exercised or not.	
☹	9 people out of 100 left the study whether they exercised or not.	
☹	**5 more** people out of 100 left the study in the lower limb exercise group.	
Chance: Safety		
14% patients in exercise group stopped due to intolerable pain during exercise.		
Chance: Adherence		
The number of people who adhered to resistance exercise was not reported.		

Step 3: GRADE Evidence profile
See Table 1 d: Resistance land-based exercise versus usual care

Step 4: Other recommendations

Group	Recommendation
AAOS (knee only)	We recommend patients with symptomatic OA of the knee be encouraged to participate in low-impact aerobic fitness exercises. Range of motion/flexibility exercises are an option for patients with symptomatic OA of the knee. We suggest quadriceps strengthening for patients with symptomatic OA of the knee.
EULAR	Non-pharmacological treatment of knee OA should include education, *exercise*, appliances (sticks, insoles, knee bracing) and weight reduction.
OARSI	Patients with hip and knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle strengthening and range of motion exercises. For patients with systematic hip OA, exercises in the water can be effective.

Step 5: GRADE Recommendation

References
Fransen M, McConnell S. Exercise for osteoarthritis of the knee. Cochrane Database of Syst Rev 2008;(4):CD004376.

Huang MH, Lin YH, Lee CL, Yang RC. Use of ultrasound to increase effectiveness of idokinetic exercise for knee osteoarthritis. Arch Phys Med Rehabil 2005;86(8):1545-51.

1.3 Aquatic exercises

1.3.1 Aquatic exercise versus no exercise for OA of hip or knee

Is aquatic exercise effective in reducing pain and improving function in patients with symptomatic knee and hip OA compared to usual care?
Interventions description: All types of exercises developed in the therapeutic/heated indoor pool (range of motion, dynamics, aerobics, etc.).

Step 1: Search Results
Only one meta-analysis was found that assessed aquatic exercise for knee osteoarthritis (Bartels, 2007). Two more recent randomized controlled trials were also found (Lund, 2008; Gill, 2009). Although Lund (2008) found no improvement following aquatic exercise, Gill (2009) found similar results to those reported below whereby pain was decreased.

**** NOTE:** This evidence is the same as that found in the hip exercise summary of findings because data from both joints were pooled******

Step 2: GRADE Summary of findings

	aquatic exercise compared to no exercise for osteoarthritis of hip or knee						
	Patient or population: patients with osteoarthritis of hip or knee **Settings:** **Intervention:** aquatic exercise **Comparison:** no exercise						
Outcomes	**Illustrative comparative risks* (95% CI)** Assumed risk **no exercise**	Corresponding risk **aquatic exercise**	**Relative effect (95% CI)**	**Absolute difference**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**NNT**
Benefits							

Pain after intervention Pooled different scales[1]	34%	41% of those in aquatic exercise group experienced a decrease in pain (35% to 48%)	1.2	7%	638 (4[3])	⊕⊕⊕⊕ **high**[2]	11 (6 to 52)
Pain follow up WOMAC pain . Scale from: 0 to 20. (follow-up: mean 6 months)	34%	39%[4] (30% to 47%)	1.1	4%	310 (1[5])	⊕⊕⊕⊕ **high**[2]	Not statistically significant
Function after intervention Pooled different scales[1]	36%	46% (40% to 52%)	1.3	10%	648 (4[3])	⊕⊕⊕⊕ **high**[2]	8 (5 to 19)
Function follow up WOMAC physical function. Scale from: 0 to 68. (follow-up: mean 6 months)	36%	39% (31% to 48%)	1.1	4%	306 (1[5])	⊕⊕⊕⊕ **high**[2]	Not statistically significant
Harms							
Withdrawals follow up total withdrawals (follow-up: mean 18 months)	29%	35% (25 to 48%)	**RR 1.2** (0.86 to 1.66)	6%	312 (1[5])	⊕⊕⊕⊕ **high**[2]	Not statistically significant
Adherence	Found 59% adherence to aquatic exercise intervention[5].						
Safety	Not reported						

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Pooled different scales including WOMAC, VAS, HAQ
[2] Patients not blinded to treatment as it is impossible to do so, therefore we did not downgrade
[3] Cochrane 2005, Foley 2003, Wang 2004, Patrick 2001
[4] This RCT had a significant SMD immediately after intervention
[5] Cochrane 2005

Visual Summary of Findings Table

Aquatic exercise compared to no exercise for osteoarthritis of hip or knee Chance: Improving pain immediately after aquatic exercise	
NNT: 11	
59 people out of 100 don't improve whether or not they did aquatic exercise	
34 people out of 100 improve whether or not they did aquatic exercise	
7 more people out of 100 improve with aquatic exercise	
Chance: Improving pain after 6 months	
NNT: n/a	**Not statistically significant**
61 people out of 100 don't improve whether or not they did aquatic exercise	
34 people out of 100 improve whether or not they did aquatic exercise	
5 more people out of 100 improve with aquatic exercise	
Chance: Improving function immediately after aquatic exercise	
NNT: 8	
54 people out of 100 don't improve whether or not they did aquatic exercise	
36 people out of 100 improve whether or not they did aquatic exercise	
10 more people out of 100 improve with aquatic exercise	
Chance: Improving function after 6 months	
NNT: n/a	**Not statistically significant**
61 people out of 100 don't improve whether or not they did aquatic exercise	
36 people out of 100 improve whether or not they did aquatic exercise	
3 more people out of 100 improve with aquatic exercise	

Chance: Withdrawals		
NNH: n/a		**Not statistically significant**
😐	65 people out of 100 did not leave the study whether or not they did aquatic exercise.	
☹	29 people out of 100 left the study whether or not they did aquatic exercise.	
☹	**6 more** people out of 100 left the study when they did aquatic exercise.	
Chance: Safety		
Safety of aquatic exercise was not reported.		
Chance: Adherence		
41 people out of 100 did not adhere to aquatic exercise.		

Step 3: GRADE Evidence profile
See Table 1 e: Aquatic exercise versus no exercise for OA of hip or knee

Step 4: Other recommendations

Group	Recommendation
AAOS (knee only)	We recommend patients with symptomatic OA of the knee be encouraged to participate in low-impact aerobic fitness exercises. Range of motion/flexibility exercises are an option for patients with symptomatic OA of the knee. We suggest quadriceps strengthening for patients with symptomatic OA of the knee.
EULAR	Non-pharmacological treatment of knee OA should include education, *exercise*, appliances (sticks, insoles, knee bracing) and weight reduction.
OARSI	Patients with hip and knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle strengthening and range of motion exercises. For patients with systematic hip OA, exercises in the water can be effective.

Step 5: GRADE Recommendation

References

Bartels ME, Lund H, Hagen KB, Dagfinrud H, Christensen R, Danneskiold-Samsoe B. Aquatic exercise for the treatment of knee and hip osteoarthritis. Cochrane Database of Syst Rev 2007(4):CD005523.

Cochrane T, Davey RC, Matthes Edwards SM. Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis. Health Technol Assess 2005;9(31):iii-xi, ix-xi, 1-114.

Wyatt FB, Milam S, Manske RC, Deere R. The effects of aquatic and traditional exercise programs on programs on persons with knee osteoarthritis. J Strength Cond Res 2001;15(3):337-40.

1.3.2 Aquatic exercise versus land-based exercise of knee OA

Is aquatic exercise effective in reducing pain and improving function in patients with symptomatic knee OA compared to land-based exercise?

Step 1: Search Results

Only one SR was found considering aquatic exercise for knee osteoarthritis (Bartels, 2007). This SR included only one RCT analyzing aquatic exercise vs. land-based exercise for knee OA (Wyatt, 2001).

Interventions description: All types of exercises developed in the therapeutic/heated indoor pool (range of motion, dynamics, aerobics, etc.).

Step 2: GRADE Summary of findings

	aquatic exercise compared to land exercise for osteoarthritis of the knee						
	Patient or population: patients with osteoarthritis of the knee **Settings:** **Intervention:** aquatic exercise **Comparison:** land exercise						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Absolute difference**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**NNT**
	Assumed risk **land exercise**	Corresponding risk **aquatic exercise**					
Benefits							

pain VAS. Scale from: 0 to 10. (follow-up: mean 6 weeks)	32%	65% of those in aquatic exercise group experienced a decrease in pain (41% to 84%)	2.0	33%	46 (1[4])	⊕OOO **very low**[1,2,3]	3 (2 to 9)
function - walking ability timed 1-mile walk. Scale from 0 to 25 min (follow-up: mean 6 weeks)	15%	28% (12% to 50%)	1.9	13%	46 (1[4])	⊕OOO **very low**[1,2,3]	Not statistically significant
Harms							
Withdrawals	4 out of 46 subjects withdrew due to illness[5]						
Adherence	Not reported						
Safety	Not reported						

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Concealment of allocation was unclear
[2] no comparision to placebo
[3] Only end-of-study data could be reported here and N is low (n=42) and large CI
[4] Wyatt 2001
[5] RCT does not specify to which group they pertained

Visual Summary of Findings Table
Aquatic exercise compared to land exercise for osteoarthritis of the knee

Chance: Improving pain after 6 weeks	
NNT: 3	
35 people out of 100 don't improve with either type of exercise	
32 people out of 100 improve with either type of exercise	
33 more people out of 100 improve with aquatic exercise.	
Chance: Improving function (ability to walk) after 6 weeks	
NNT: n/a	**Not statistically significant**
72 people out of 100 don't improve with either type of exercise	
15 people out of 100 improve with either type of exercise	
13 more people out of 100 improve with aquatic exercise	
Chance: Withdrawls	
4 out of 46 people withdrew due to illness.	
Chance: Safety	
Safety was not reported.	
Chance: Adherence	
The number of people who adhered to the exercise programs was not reported.	

Step 3: GRADE Evidence profile
See Table 1 f: Aquatic exercise versus land-based exercise for knee OA

Step 4: Other recommendations

Group	Recommendation
AAOS (knee only)	We recommend patients with symptomatic OA of the knee be encouraged to participate in low-impact aerobic fitness exercises. Range of motion/flexibility exercises are an option for patients with symptomatic OA of the knee. We suggest quadriceps strengthening for patients with symptomatic OA of the knee.
EULAR	Non-pharmacological treatment of knee OA should include education, *exercise*, appliances (sticks, insoles, knee bracing) and weight reduction.
OARSI	Patients with hip and knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle strengthening and range of motion exercises. For patients with systematic hip OA, exercises in the water can be effective.

Step 5: GRADE Recommendation

References

Bartels ME, Lund H, Hagen KB, Dagfinrud H, Christensen R, Danneskiold-Samsoe B. Aquatic exercise for the treatment of knee and hip osteoarthritis. Cochrane Database of Syst Rev 2007(4):CD005523.

Wyatt FB, Milam S, Manske RC, Deere R. The effects of aquatic and traditional exercise programs on programs on persons with knee osteoarthritis. J Strength Cond Res 2001;15(3):337-40.

1.4 Tai chi

Is tai chi effective in reducing pain and improving function in patients with symptomatic knee OA compared to usual care?

Step 1: Search Results
One systematic review (Lee 2008) assessed the effect of tai chi in patients with both hip and knee OA. However, results of the 5 included RCTs and 7 non-randomized studies were not pooled due to high heterogeneity. Therefore, we chose the RCT from this systematic review which most closely matched our PICO question by having an appropriate control group and with the largest sample size. The RCT by Brismee, 2007 was the closest match to having a control group (defined as "attention control in Brismee 2007) since the other studies had control groups of hydrotherapy, routine care and bingo.

Intervention description: Simplified Yang-style tai chi with instructor three times a week for six weeks followed by six weeks with home video.

Note: the study included has a sample size of 31 people, and 24% of the participants were lost to follow-up.

Step 2: GRADE Summary of findings

	Tai chi compared to no exercise (education on OA) for knee OA						
	Patient or population: patients with osteoarthritis of the knee **Settings:** **Intervention:** tai chi **Comparison:** no exercise (education on OA)						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Absolute difference**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**NNT**
	Assumed risk **no exercise (education on OA)**	Corresponding risk **Tai chi**					
Benefit							
Pain WOMAC . Scale from: 0 to 35. (follow-up: mean 12 weeks)	33%	35% of those in tai chi group experienced a decrease in pain (11% to 58%)	2%	1.1	31 (1[2])	⊕⊕OO **low**[1]	Not statistically significant

Function WOMAC. Scale from: 0 to 85. (follow-up: mean 12 weeks)	33%	35% (11% to 58%)	2%	1.1	31 (1[2])	⊕⊕OO **low**[1]	Not statistically significant
Harms							
Withdrawals Number of drop-outs (follow-up: mean 12 weeks)	**32%**	**18%** (6 to 55%)	**RR 0.58** (0.19 to 1.74)	13%	41 (1[2])	⊕⊕⊕O **moderate**[1]	Not statistically significant **(Note: more people in the control group withdrew from the study)**
Adherence	90% adherence in tai chi group						
Safety	Not reported						

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Large CI and small N=35
[2] Brismee, 2007

Visual Summary of Findings Table

Tai chi compared to no exercise (education on OA) for osteoarthritis of the knee

Chance: Improving pain		
NNT: n/a		**Not statistically significant**
😐	65 people out of 100 don't improve with either treatment.	
🙂	33 people out of 100 improve with either treatment.	
🙂	**2 more people** out of 100 improve with tai chi.	
Chance: Improving function		
NNT: n/a		**Not statistically significant**
😐	65 people out of 100 don't improve with either treatment.	
🙂	33 people out of 100 improve with either treatment.	
🙂	**2 more people** out of 100 improve with tai chi.	
Chance: Withdrawals*		
NNH: n/a		**Not statistically significant (Note: more people in the control group withdrew from the study)**
😐	68 people out of 100 did not leave the study with either treatment.	
☹	18 people out of 100 left the study with either treatment.	
☹	**13 more** people out of 100 left the study in the control group than the tai chi.	
Chance: Safety		
Safety of tai chi was not reported.		
Chance: Adherence		
90% of people in the tai chi group adhered to the program.		

*does not add up to 100 due to rounding

Step 3: GRADE Evidence profile

See Table 1 g: Tai Chi compared to no exercise (education on OA) for knee OA

Step 4: Other recommendations

Group	Recommendation
AAOS (knee only)	We recommend patients with symptomatic OA of the knee be encouraged to participate in low-impact aerobic fitness exercises. Range of motion/flexibility exercises are an option for patients with symptomatic OA of the knee. We suggest quadriceps strengthening for patients with symptomatic OA of the knee.
EULAR	Non-pharmacological treatment of knee OA should include education, *exercise*, appliances (sticks, insoles, knee bracing) and weight reduction.
OARSI	Patients with hip and knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle strengthening and range of motion exercises. For patients with systematic hip OA, exercises in the water can be effective.

Step 5: GRADE Recommendation

References

Brismee JM, Paige RL, Chyu MC, Boatright JD, Hagar JM, McCaleb JA, Quintela MM, Feng D, Xu KT, Shen CL. Group and home-based tai chi in elderly subjects with knee osteoarthritis: a randomized controlled trial. Clin Rehabil 2007;21:99-111.

Lee MS, Pittler MH, Ernst E. Tai chi for osteoarthritis: a systematic review. Clin Rheumatol 2008;27(2):211-8.

1.5 General hip exercise

Is exercise effective in reducing pain and improving function in patients with symptomatic hip osteoarthritis (OA) compared to usual care?

Step 1: Search Results
One meta-analysis (Hernandez-Molina, 2008) was found which pooled land-based, aquatic, and tai chi exercises. The remaining RCTs found which were not included in the meta-analysis did not follow the guideline's inclusion criteria since they were post-operative interventions.

Intervention description: For the pain outcome, the systematic review (SR) included any exercise program of at least 4 weeks duration (Hernandez-Molina, 2008). For the function outcome, "The exercise group performed water and land-based exercise 3 times weekly over a 6-week period immediately prior to surgery. During the first 3 weeks, participants performed 1–2 sets of 8–12 repetitions of single-joint movements while standing in chest-deep, 93°F water. Pool exercises focused on single planar motion of the cervical spine, shoulders, elbows, wrists, hands, hips, knees, and ankles. During weeks 4–6, exercise sessions involved a total body fitness program of cardiovascular, strength, and flexibility training" (Rooks, 2006).

Step 2: GRADE Summary of findings

	exercise compared to no exercise for osteoarthritis of the hip						
	Patient or population: patients with osteoarthritis of the hip **Settings:** **Intervention:** exercise **Comparison:** no exercise						
Outcomes	**Illustrative comparative risks* (95% CI)** Assumed risk **no exercise**	Corresponding risk **exercise**	**Relative effect (95% CI)**	**Absolute difference**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**NNT**
Benefit							
Pain pooled WOMAC and VAS . Scale from: 0 to 100. (follow-up: 3-18 months)	34%	56% of those in any exercise group experienced a decrease in pain (38% to 100%)	1.6	22%	310 (7[2])	⊕⊕⊕O **moderate**[1]	4 (2 to 18)
Function	Not reported						
Harms							
Safety	Not reported						

Withdrawals	Not reported
Adherence	Not reported
	*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). CI: Confidence interval;
	GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.
	[1] although Isquared = 0, different interventions pooled, including aquatic, tai chi, and land exercise. [2] Fransen 2007, Rooks 2006, Cochrane 2005, Tak 2005, Foley 2003, Hopman-Rock 2000, Van Baar 1998.* Hinman 2007 was not included in analysis since hip was not index joint and Ravaud 2007 was not included in analysis because it created large heterogeneity.

Visual Summary of Findings Table
Exercise compared to no exercise for osteoarthritis of the hip

Chance: Improving pain after 3-18 months	
NNT: 4	
😐 44 people out of 100 don't improve whether or not they exercise	
☺ 34 people out of 100 improve whether or not they exercise	
☺ **22 more people** out of 100 improve with exercise	
Chance: Improving function after 3-18 months	
Improvement in function with exercise was not reported	
Chance: Withdrawls	
The number of people who left the study was not reported.	
Chance: Safety	
Safety of exercise was not reported.	
Chance: Adherence	
Adherence to exercise was not reported.	

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Step 3: GRADE Evidence profile
See Table 1 h: Exercise compared to no exercise for osteoarthritis of the hip

Step 4: Other recommendations

Group	Recommendation
EULAR	Non-pharmacological treatment of knee OA should include education, *exercise*, appliances (sticks, insoles, knee bracing) and weight reduction.
OARSI	Patients with hip and knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle strengthening and range of motion exercises. For patients with systematic hip OA, exercises in the water can be effective.
AAOS (knee only)	We recommend patients with symptomatic OA of the knee be encouraged to participate in low-impact aerobic fitness exercises. Range of motion/flexibility exercises are an option for patients with symptomatic OA of the knee. We suggest quadriceps strengthening for patients with symptomatic OA of the knee.

Step 5: GRADE Recommendation

References

Hernandez-Molina G, Reichenbach S, Zhang B, Lavalley M, Felson DT. Effect of Therapeutic Exercise for Hip Osteoarthritis Pain: Results of a Meta-analysis. Arthritis & Rheum 2008;59(9):1221-8.

Rooks DS, Huang J, Bierbaum BE, Bolus SA, Rubano J, Connolly CE, et al. Effect of preoperative exercise on measures of functional status in men and women undergoing total hip and knee arthroplasty. Arthritis Rheum 2006;55:700-8.

2. INSOLES

2.1 Laterally wedged insoles versus neutrally wedged insoles for knee OA

Are laterally wedged insoles effective in reducing pain and improving function in patients with symptomatic medial compartment knee OA compared to neutrally wedged insoles? Are patients adherent to these treatment regimens?

Step 1: Search Results

We chose Brouwer, 2008 for lateral wedge insoles since it is the most recent and relevant SR (SR). This SR reported only one RCT comparing laterally and neutrally wedged insoles: Maillefert, 2001.

Intervention description: Insoles were made of Ledos material (Société Française d'Orthopodie, Paris, France), mounted on a leather strip. The Ledos material is made of pure rubber with cork powder, and has a great capacity to absorb impact loading. The laterally elevated insoles were individually modeled, with elevation depending on static pedometer evaluation, but without any biomechanical evaluation during walking.

Step 2: GRADE Summary of findings

Laterally wedged insoles compared to neutrally wedged insoles for painful medial knee osteoarthritis

Patient or population: patients with painful medial Knee OA
Intervention: Laterally wedged insoles
Comparison: neutrally wedged insoles

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **neutrally wedged insoles**	Corresponding risk **Laterally wedged insoles**					
Benefits							
Pain WOMAC. Scale from: 0 to 100. (follow-up: 6 months)	35%[1]	25% (16% to 36%)	-10%	0.71	147 (1)	⊕⊕OO low[2,3]	Not statistically significant *Laterally wedged insoles show less improvement in pain than neutrally wedged insoles.
Physical function WOMAC. Scale from: 0 to 100. (follow-up: mean 6 months)	35%[4]	25% (16% to 37%)	-10%	0.71	147 (1)	⊕⊕OO low[2,3]	Not statistically significant *Laterally wedged insoles show less improvement in function than neutrally wedged insoles.
Harms							
Adherence number of patients who wore insoles permanently during the study period (follow-up: 6 months)	74%	88% (75% to 100%)	14%	1.18 (1.01 to 1.38)	156 (1)	⊕⊕⊕O moderate[2]	7 (4 to 135) *Laterally wedged insoles show better compliance than neutrally wedged insoles.
Withdrawals due to intolerance to the treatment number of patients who withdrew from the study because of intolerance to the treatment (follow-up: 6 months)	1%	0% (0% to 10%)	-1%	0.30 (0.01 to 7.28)	156 (1)	⊕⊕OO low[2,3]	Not statistically significant *Laterally wedged insoles show less withdrawals due to intolerance than neutrally wedged insoles.

[1] This SMD was calculated using RevMan 5 with the 6-month end of study data. WOMAC pain was more decreased in the neutrally wedged group than the laterally wedged group. This result along with those at 1, 3, 12 and 24 months is not statistically significant.
[2] The randomization procedure and allocation concealment were not described. The trial (Maillefert, 2001) did not blind the outcome assessors and the care providers. The insoles were individually modeled and therefore the intervention was not identical for all patients. The quality assessment score was not reduced because of this.
[3] The confidence interval ranges from not being clinically significant to a very large clinical effect, which is a sign of imprecision.
[4] This SMD was calculated using RevMan 5 with the 6-month end of study data. WOMAC function was more decreased in the laterally wedged group than the neutrally wedged group. This result along with those at 1, 3, 12 and 24 months is not statistically significant.

Visual Summary of findings figure:
Laterally wedged insoles compared to neutrally wedged insoles for painful medial Knee OA

Chance: Improving pain and physical function (6 Months)	
NNT: Not statistically significant	Not statistically significant
😐 65 people out of 100 don't improve	
☺ 25 people out of 100 improve either type of insole	
☹ **10 fewer people** out of 100 improve with laterally wedged insoles	
Chance: Adherence (6 months): number of patients who wore insoles permanently during the study period	
NNH: 7	
😐 74 people out of 100 wore either type of insole permanently during the study period.	
☹ 12 people out of 100 did not wear either type of insole permanently during the study period.	
☹ **14 fewer people** out of 100 wore neutrally wedged insoles permanently during the study period.	
Chance: Withdrawing from the trials after 6 months because of intolerance to the treatment.	
NNH: Not statistically significant	**Not statistically significant**
😐 99 out of 100 people did not drop out of the trials	
☹ 0 out of 100 people dropped out with either type of insole	
☹ 1 **more person** out of 100 dropped out with neutrally wedged insoles.	

Step 3: GRADE Evidence profile

See Table 2 a: Laterally wedged insoles versus neutrally wedged insoles

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	We suggest *lateral heel wedges not be prescribed* for patients with symptomatic medial compartmental OA of the knee.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, *insoles*, knee bracing) and weight reduction.
OARSI	Every patient with hip and knee OA should receive advice concerning appropriate footwear. In patients with knee OA, *insoles* can reduce pain and improve ambulation. Lateral wedged insoles can be of symptomatic benefit for some patients with medial tibio-femoral compartment OA.

Step 5: GRADE Recommendation

References

Brouwer RW, Jakma TS, Verhagen AP, Verhaar JA, Bierma-Zeinstra SM. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database of Syst Rev 2005;(1):CD004020.

Maillefert JF, Hudry C, Baron G et al. Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis: a prospective randomized controlled study. Osteoarthritis Cartilage 2001;9(8):738-45.

2.2 Medial wedged insoles versus neutrally wedged insoles for knee OA

Are medial wedged insoles effective in reducing pain and improving function in patients with symptomatic lateral compartment knee OA compared to neutrally wedged insoles?

Step 1: Search Results

We chose Rodrigues, 2008 for medial wedged insoles since it is the only RCT we found in the literature review and no SRs have been done on the subject.

Intervention description: The medial insole group wore 8-mm-high medial-wedge insoles for the rearfoot inserted into a new shoe for 8 weeks. The neutral insole group wore an insole resembling that of the former group but without raised wedges for 8 weeks. Patients of both groups received the same new shoe and were blind to insole use. The ethylene-vinyl-acetate (density 50) insoles were provided by the AACD Institute (Associaçao de Assistência à Criança Deficiente). A commercial neoprene with elastic banding was used for ankle support. Both groups used similar standard shoes supplied by the hospital. Each participant was instructed to use the splints (shoes and elastic banding) for 3–6 hours daily.

Step 2: GRADE Summary of findings

*This study has a very small sample size (n=30), which could undermine its validity.

Medially wedged insoles compared to neutrally wedged insoles for knee OA

Patient or population: patients with knee OA
Intervention: Medially wedged insoles
Comparison: neutrally wedged insoles

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk neutrally wedged insoles	Corresponding risk Medially wedged insoles					
Benefits							
Pain on movement VAS scale transformed into percentage of change over time. Scale from: 0 to 100. (follow-up: 8 weeks)	41%	85% (60% to 97%)[1]	44%	2.07	30 (1)	⊕⊕⊕O moderate[2]	3 (2 to 5)
Function WOMAC transformed into percentage of change over time. Scale from: 0 to 100. (follow-up: 8 weeks)	27%	86% (59% to 97%)[1]	59%	3.19	30 (1)	⊕⊕⊕O moderate[2]	2 (2 to 3)
Harms							
Mild discomfort number of patients with event (follow-up: 8 weeks)	7%	2% (0% to 47%)	-5%	0.29 (0.01 to 6.69)	30 (1)	⊕⊕OO low[2,3]	Not statistically significant
Adherence	All patients used the insoles regularly throughout the study						
Withdrawals	No withdrawals						

[1] This SMD was calculated using RevMan 5 with the percentage of change over time provided by the authors.
[2] The sample is small: 30 women with valgus knee OA. Pain at rest was statistically different at baseline.
[3] The confidence interval ranges from not being clinically significant to a very large clinical effect, which shows imprecision.

Visual Summary of findings figure:
Medially wedged insoles compared to neutrally wedged insoles for knee OA

Chance: Improving pain when moving after 8 weeks	
NNT: 3	
15 people out of 100 don't improve with either type of insole	
41 people out of 100 improve with either type of insole	
44 more people out of 100 improve with Medially wedged insoles	
Chance: Improving function after 8 weeks	
NNT: 2	
14 people out of 100 don't improve with either type of insole	
27 people out of 100 improve with either type of insole	
59 more people out of 100 improve with Medially wedged insoles	
Chance: Mild discomfort after 8 weeks	
NNH: n/a	**Not significantly significant**
93 people out of 100 avoid mild discomfort with either type of insole.	
2 people out of 100 have mild discomfort with either type of insole.	
5 more people out of 100 have mild discomfort with neutrally wedged insoles	
Chance: Adherence	
All patients used the insoles regularly throughout the study	
Chance: Withdrawls	
There were no withdrawals from the study	

Step 3: GRADE Evidence profile
See Table 2 b: Medial wedged insoles versus neutrally wedged insoles for knee osteoarthritis

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	We suggest *lateral heel wedges not be prescribed* for patients with symptomatic medial compartmental OA of the knee.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, *insoles*, knee bracing) and weight reduction.
OARSI	Every patient with hip and knee OA should receive advice concerning appropriate footwear. In patients with knee OA, *insoles* can reduce pain and improve ambulation. Lateral wedged insoles can be of symptomatic benefit for some patients with medial tibio-femoral compartment OA.

Step 5: GRADE Recommendation

References

Rodrigues PT. Effectiveness of medial-wedge insole treatment for valgus knee osteoarthritis. Arthritis and rheumatism 2008;59(5):603-8.

2.3. Subtalar strapped insoles versus inserted laterally wedged insoles for knee OA

Are subtalar strapped insoles effective in reducing pain and improving function in patients with symptomatic knee OA compared to inserted laterally wedged insoles?

Step 1: Search Results

We chose the SR by Brouwer 2008 which reported one RCT which can be found in three articles by Toda (RCT published in 2001 with follow-up data published in 2004 and 2006). We are presenting the data at 6 months follow-up for efficacy and at 8 weeks for side effects as these were the only time points at which these were evaluated respectively.

Intervention description: Radiographs were evaluated for changes characteristic of OA in anteroposterior views using the Kellgren-Lawrence grade, as described in the *Atlas of Standard Radiographs*. Two types of lateral wedge insoles were prepared: urethane wedges made from household bath mat material with elevations of 6.35 mm strapped to an ankle sprain supporter (Sofra Wolfer®, Taketora Co. Ltd., Japan) designed to fit around the ankle and subtalar joints (strapped insole, Figure 1A); and a traditional inserted insole (Wedge Heel Type®, Sanshinkousan Co. Ltd., Japan), a lateral rubber heel wedge with an elevation of 6.35 mm (inserted insole, Figure 1B). Each participant

was instructed to use the insole whenever wearing shoes, for between 3 and 6 hours each day for 8 weeks.

Step 2: GRADE Summary of findings

Subtalar strapped insoles compared to inserted laterally wedged insoles for knee OA

Patient or population: patients with knee OA
Intervention: Subtalar strapped insoles
Comparison: inserted laterally wedged insoles

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **Inserted laterally wedged insoles**	Corresponding risk **Subtalar strapped insoles**					
Benefits							
Pain visual analog scale. Scale from: 0 to 100. (follow-up: 6 months)	36%	58% (38% to 76%)[1]	22%	1.61	61 (1)	⊕⊕⊕O moderate[2]	4 (3 to 35)
Function Lequesne index (follow-up: 6 months)	37%	48% (29% to 67%)[3]	11%	1.30	61 (1)	⊕⊕⊕O moderate[2]	Not statistically significant
Harms							
Side effects number of patients with event (follow-up: 8 weeks)	2%	13% (2% to 100%)[4]	11%	5.74 (0.72 to 45.77)	90 (1)	⊕⊕OO LOW[2,6]	Not statistically significant
Withdrawals number of patients who withdrew after randomization (follow-up: 6 months)	6%	9% (2% to 53%)[5]	3%	1.59 (0.28 to 8.93)	66 (1)	⊕⊕OO LOW[2,6]	Not statistically significant
Adherence				Not reported			

[1] This SMD was calculated using Rev Man 5 with the 6-months end of study data. This result along with the one at 8 weeks are statistically significant (SMD= -0.42 (-0.83, 0)). The data at 24 month were not statistically significant.
[2] The randomization procedure was done according to birth date and the allocation concealment was not described. The trials (Toda, 2001, 2004 and 2006) did not blind the outcome assessors, the care providers or the patients.
[3] This SMD was calculated using Rev Man 5 with the 6-months end of study data. This result along with the one at 8 weeks and 24 months are not statistically significant.
[4] In the strapped insole group, 3 participants complained of popliteal pain, 2 reported low back pain and one had foot sole pain. Only one patient complained of foot sole pain in the inserted insole group. However, side effects were not severe enough to deter participants from continuing to wear the insole.
[5] People who withdrew had either moved or cited household commitments.
[6] The confidence interval ranges from not being clinically significant to a very large clinical effect, which is a sign of imprecision.

Visual Summary of findings figure:
Subtalar strapped insoles compared to inserted laterally wedged insoles for knee OA

Chance: Improving pain after 6 Months	
NNT: 4	
42 people out of 100 don't improve with either type of insole	
36 people out of 100 improve with either type of insole	
22 more people out of 100 improve with Subtalar strapped insoles	
Chance: Improving function after 6 Months	
NNT: Not statistically significant	**Not statistically significant**
52 people out of 100 don't improve with either type of insole	
37 people out of 100 improve with either type of insole	
11 more people out of 100 improve with Subtalar strapped insoles	
Chance: Side effects after 8 weeks	
NNH: Not statistically significant	**Not statistically significant**
87 out of 100 people avoid side effects	
2 out of 100 people had side effects with either type of insole	
11 more people out of 100 had side effects with Subtalar strapped insoles	
Chance: Withdrawing from the trials after 6 months	
NNH: Not statistically significant	**Not statistically significant**
91 out of 100 people did not drop out of the trials	
6 out of 100 people dropped out with either type of insole	
3 more people out of 100 dropped out with Subtalar strapped insoles	

Chance: Adherence	
Adherence was not reported	

Step 3: GRADE Evidence profile
See Table 2 c: Subtalar strapped insoles versus inserted laterally wedged insoles

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	We suggest *lateral heel wedges not be prescribed* for patients with symptomatic medial compartmental OA of the knee.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, *insoles*, knee bracing) and weight reduction.
OARSI	Every patient with hip and knee OA should receive advice concerning appropriate footwear. In patients with knee OA, *insoles* can reduce pain and improve ambulation. Lateral wedged insoles can be of symptomatic benefit for some patients with medial tibio-femoral compartment OA.

Step 5: GRADE Recommendation

References

Brouwer RW, Jakma TS, Verhagen AP, Verhaar JA, Bierma-Zeinstra SM. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database of Syst Rev 2005;(1):CD004020.

Toda Y, Tsukimura N. A six-month followup of a randomized trial comparing the efficacy of a lateral-wedge insole with subtalar strapping and an in-shoe lateral-wedge insole in patients with varus deformity osteoarthritis of the knee. Arthritis Rheum 2004; 50(10):3129-3136.

Toda Y. A 2-year follow-up of a study to compare the efficacy of lateral wedged insoles with subtalar strapping and in-shoe lateral wedged insoles in patients with varus deformity osteoarthritis of the knee. Osteoarthritis and cartilage / OARS , Osteoarthritis Research Society 2006;14(3):231-7.

Toda Y, Segal N, Kato A, Yamamoto S, Irie M. Effect of a novel insole on the subtalar joint of patients with medial compartment osteoarthritis of the knee. J Rheumatol 2001; 28(12):2705-2710

TABLE 1. Lower Extremity Kinesthesia and Balance Exercises Used in the Study

1. Week	1. Modified Romberg exercise (standing in balance with eyes closed)
	a) On hard ground
	b) On soft ground (on a mat)
	2. Retrowalking (25 m)
	3. Walking on heels (25 m)
	4. Walking on toes (25 m)
	5. Walking with eyes closed (25 m)
	6. Standing on one extremity for 30 seconds (repeated in both extremities)
	Leaning forward, backward, and to the sides on one extremity (eyes open)
	Leaning forward, backward, and to the sides on one extremity (eyes closed)
	Sitting down and standing up from a high chair slowly
2. Week (in addition)	1. Exercise with "rocker-bottom" balance board
	2. Sitting down and standing up from a low chair slowly
	3. Plyometric exercise (crossing a height of 15 cm by jumping)
	4. 8 exercise
	a) Walking slowly, wide circle
	b) Walking quickly, wide circle
	c) Walking slowly, narrow circle
	d) Walking quickly, narrow circle
3. Week (in addition)	1. Exercise with "BAPS board" balance board
	a) Balance with 2 legs, eyes open, multidirectional
	b) Balance with 2 legs, eyes closed, multidimensional
	c) Balance with one leg, eyes open, unidimensional
	d) Balance with one leg, eyes closed, unidimensional
	e) Balance with one leg, eyes open, multidimensional
	f) Balance with one leg, eyes closed, multidimensional
	2. Minitrampoline exercise (jumping and jogging)
	3. Plyometric exercise (crossing a height of 15 cm by jumping)
	4. Carioca crossover maneuver

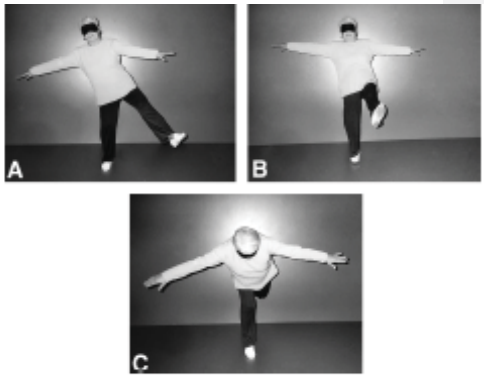


FIGURE 1. (A) Balance exercise toward the sides on a single foot while the eyes are closed. (B) Balance exercise toward the back on a single foot while the eyes are closed. (C) Balance exercise toward the front on a single foot while the eyes are closed.

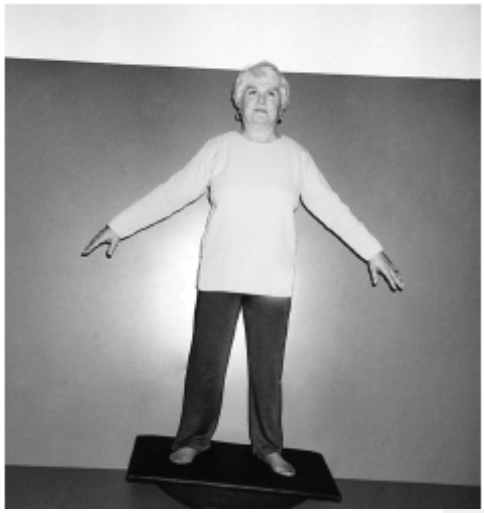


TABLE 2. Lower Extremity Isometric and Isotonic Strengthening Program Used in the Study

1. Week	1. 5-min fixed bike exercise without resistance
	2. Range-of-motion and active stretching exercises applied to hamstring and quadriceps muscles
	3. Quadriceps isometric strengthening exercise
	4. Hamstring muscles isometric exercise
2. Week (in addition)	1. Short-arc terminal extension exercise for the knee joint
	2. Isometric exercise for the abductor and adductor muscles of the hip joint
3. Week (in addition)	1. Short-arc terminal extension exercise with resistance for the knee joint
	2. Isometric strenghtening exercise with resistance for the hamstring muscles

3. SELF-MANAGEMENT

Are self-management programs effective in reducing pain and improving function in patients with symptomatic knee osteoarthritis (OA) compared to usual care?

Step 1: Search Results
Three meta-analyses on self-management programs were found (Chodosh, 2005; Devos-Comby, 2006; Warsi, 2004). Although Devos-Comby (2006) was the most recent evidence, exercise and self-management were presented such that outcomes from each intervention could not be separated. Warsi (2004) did not focus on OA. Chodosh (2005) met our selection criteria and was therefore chosen as the best available evidence. Devos-Comby (2006) had similar results to Chodosh (2005), whereby, no clinically significant effect was found on physical outcomes.

Interventions description: Chronic disease self-management program was defined by the authors of the systematic review as "a systematic intervention that is targeted toward patients with chronic disease. The intervention should help them actively participate in either or both of the following: self-monitoring (of symptoms or of physiologic processes) or decision making (managing the disease or its impact through self-monitoring)" (Chodosh, 2005).

Step 2: GRADE Summary of findings

Self-management program compared to no self-management for knee OA

Patient or population: patients with Osteoarthritis
Intervention: Self-management program
Comparison: no self-management

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk no self-management	Corresponding risk Self-management program	Relative effect (95% CI)	Absolute difference	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
Benefit							
pain Not specified but likely pooled several different scales (follow-up: 2-6 months)	41%	43% of those in self-management program group experienced a decrease in pain (41% to 44%)	1.05	2%	Not available	⊕⊕OO LOW	36 (22 to 108)
function Not specified but likely pooled several different scales (follow-up: 2-6 months)	31%	33% (31% to 34%)	1.06	2%	Not available	⊕⊕OO LOW	34 (21 to 103)
Harms							
safety			Not reported				
adherence			Not reported				
withdrawals			Not reported				

NOTE 1: *Although we acknowledge that psychological outcomes are relevant to self-management interventions, we decided a priori to focus only on effects on pain and function outcomes. Chodosh (2005) did not report any psychological outcomes. Devos-Comby (2006) found that although psychological outcomes were significantly improved, perceived psychological health was not statistically different.*

NOTE 2: *There was a rigorous exchange of ideas between Drs. Holman and Lorig and the authors of Chodosh (2005). The conclusion was that increased evidence is needed on the different types of self-management programs as well as long term data. This exchange can be found at* http://www.annals.org/cgi/content/abstract/143/6/427

Visual Summary of Findings Table
Self-management program compared to no self-management for osteoarthritis

Chance: Improving pain after 8 weeks	
NNT: 6	
57 people out of 100 don't improve whether they take a self management program or not	
41 people out of 100 improve with either intervention	
2 more people out of 100 improve with a self-management program	
Chance: Improving function after 8 weeks	
NNT: 6	
67 people out of 100 don't improve whether they take a self management program or not	
31 people out of 100 improve with either intervention	
2 more people out of 100 improve with a self-management program	
Chance: Safety, Adherence, Withdrawals	
NNH: n/a The safety of self-management and the number of people who adhered to a self-management program and the number of people who withdrew from self management programs was not reported.	**Not reported**

Step 3: GRADE Evidence profile
See Table 3: Self-management

NOTE: Post-hoc tests including 5 essential elements (tailoring, group setting, feedback, psychological, and medical care) were unrevealing.

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	• We suggest patients with symptomatic OA of the knee be encouraged to participate in self-management educational programs such as those conducted by the Arthritis Foundation, and incorporate activity modifications (e.g. walking instead of running; alternative activities) into their lifestyle. • Regular contact to promote self-care is an option for patients with symptomatic OA of the knee. (No recommendations for hip).
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, insoles, knee bracing) and weight reduction.
OARSI	• Optimal management of OA requires a combination of non-pharmacological and pharmacological modalities. • All patients with hip and knee OA should be given information access and education about the objectives of treatment and the importance of changes in lifestyle, exercise, pacing of activities, weight reduction, and other measures to unload the damaged joint(s). The initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health professionals. Subsequently emphasis should be placed on encouraging adherence to the regimen of non-pharmacological therapy. • The clinical status of patients with hip or knee OA can be improved if patients are contacted regularly by phone.

Step 5: GRADE Recommendation

References

Chodosh J, Morton S, Mojica W, Maglione M, Suttorp M, Hilton L, Rhodes S, Shekelle P. Meta-analysis: Chronic disease self-management programs for older adults. Ann Int Med 2005;143(6):427-38.

Devos-Comby L, Cronan T, Roesch SC. Do exercise and self-management interventions benefit patients with osteoarthritis of the knee? A metaanalytic review. J Rheumatol 2006;33(4):744-56.

Lorig KR, Sobel DS, Stewart AL, Brown BW Jr., Bandura A, Ritter P, et al. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization : a randomized trial. Med Care 1999;37(1):5-14.

Warsi A, Wang PS, L Valley MP, Avorn J, Solomon DH. Self-management education programs in chronic disease: a systematic review and methodological critique of the literature. Arch Intern Med 2004;164(15):1641-49.

4. MANUAL THERAPY

4.1 Manual therapy program versus exercise therapy program for hip OA

Is manual therapy effective in reducing pain and improving function in patients with symptomatic hip osteoarthritis (OA) compared to exercise therapy? Are patients compliant to these treatment regimens and do they experience adverse effects?

Step 1: Search Results
There were no meta-analyses which reported the efficacy of manual therapy in patients with hip OA. There was one RCT which assessed the efficacy of manual therapy vs. exercise therapy in patients with hip OA: Hoeksma (2004).

Intervention description: Subjects in both the manual therapy program and the exercise therapy program attended 25-minute sessions twice a week for a total of 9 treatments. Manual therapy consists of manipulation and stretching with the aim of improving the elasticity of the joint capsule and surrounding muscles. Each manual therapy session began with 10 to 15 minutes of stretching of shortened muscles. Manipulation was then performed using a traction manipulation technique.
The exercise therapy program was tailored to each individual participant's needs. The 4 main treatment goals were 1) increase of muscle function through muscle strengthening exercises using weight or strengthening equipment; endurance by treadmill walking of cycling on a home trainer; and coordination by walking and balancing exercises; 2) improvement of range of joint motion by motions that go beyond the daily activity range of motion and stretching; 3) decrease of pain through active joint and stretching exercises as well as second and third degree traction; 4) improvement of walking ability through specific walking exercises to adjust gait pattern, use of walking aids, and stair-climbing instruction.

In both groups, participants also received education and advice on the load ability of the hip joint and increasing their physical activity. The exercise group received additional instruction for home exercise, based on the specific exercises performed during the treatment session.

Further details about the treatment programs are described on the pages following the results.

Step 2: GRADE Summary of findings

Manual therapy compared to exercise therapy for hip OA

Patient or population: patients with hip OA
Intervention: manual therapy
Comparison: exercise therapy

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **exercise therapy**	Corresponding risk **manual therapy**					
Benefits							
Pain at rest VAS. Scale from: 0 to 100. Follow-up: 5 weeks	35%	54% (38% to 69%)[1]	19%	1.54	103 (1 study)	⊕⊕⊕⊕ high[2]	5 (3 to 27)
Physical function SF-36 Scale from: 0 to 100. Follow-up: 5 weeks	35%	39% (26% to 55%)[1]	4%	1.11	103 (1 study)	⊕⊕⊕O moderate[2,3]	Not statistically significant
Pain at rest VAS. Scale from: 0 to 100. Follow-up: 29 weeks	40%	50% (34% to 66%)[4]	10%	1.25	89 (1 study)	⊕⊕⊕O moderate[2,3]	Not statistically significant
Physical function SF-36 Scale from: 0 to 100. Follow-up: 29 weeks	35%	45% (29% to 62%)[4]	10%	1.29	88 (1 study)	⊕⊕⊕O moderate[2,3]	Not statistically significant
Harms							
Lack of adherence number of patients who prematurely discontinued the treatment programs Follow-up: 5 weeks	6%	7% (2% to 31%)	1%	1.26 (0.30 to 5.37)	109 (1 study)	⊕⊕⊕O moderate[2,3]	Not statistically significant
Adverse effects number of patients who discontinued the treatment programs because of increase of complaints[5]	4%	5% (1% to 31%)	1%	1.42 (0.25 to 8.16)	109 (1 study)	⊕⊕⊕O moderate[2,3]	Not statistically significant
Losses to follow-up number of patients who were lost to follow-up Follow-up: 29 weeks	17%	21% (10% to 47%)	4%	1.26 (0.58 to 2.75)	109 (1 study)	⊕⊕⊕O moderate[2,3]	Not statistically significant

[1] This SMD was calculated with RevMan 5 with the end-of-study data at the end of the treatment period (5-weeks).

[2] This trial was a single-blind study. The authors mention that it was not possible to blind either patients or therapists for the allocated treatment. Therefore, extra attention was given to the blinding of the outcome assessor. A placebo effect may also be present in this study due to the nature of the interventions. Finally, a limitation of the study is the relatively large number of patients who received total hip arthroplasty during the follow-up period. However, no significant differences were found between the conclusions based on the intention-to-treat analysis and the per-protocol analysis. The quality of the study was not downgraded because of these reasons.
[3]The confidence interval ranges from not being clinically significant to a very large clinical effect, which is a sign of imprecision.
[4] This SMD was calculated with RevMan 5 with the end-of-study data at 29 weeks of follow-up.
[5] In the exercise program, one patient also discontinued treatment because of cardiorespiratory disease.

Visual Summary of Findings Table
Manual therapy compared to exercise therapy for hip OA

Chance: Improving pain at rest after 5 weeks		
NNT: 5		
😐	46 people out of 100 don't improve with either treatment	
🙂	35 people out of 100 improve with either treatment	
🙂.	**19 more people** out of 100 improve with manual therapy	
Chance: Improving pain at rest after 29 weeks		
NNT: n/a		**Not statistically significant**
😐	50 people out of 100 don't improve with either treatment	
🙂	40 people out of 100 improve with either treatment	
🙂	**10 more people** out of 100 improve with manual therapy	
Chance: Improving function after 5 weeks		
NNT: n/a		**Not statistically significant**
😐	61 people out of 100 don't improve with either treatment	
🙂	35 people out of 100 improve with either treatment	
🙂.	**4 more people** out of 100 improve with manual therapy	
Chance: Improving function after 29 weeks		
NNT: n/a		**Not statistically significant**
😐	55 people out of 100 don't improve with either treatment	

	35 people out of 100 improve with either treatment	
	10 more people out of 100 improve with manual therapy	
Chance: Lack of adherence; discontinuation of therapy after 5 weeks		
NNH: n/a		
	93 people out of 100 continued with either treatment	**Not significantly significant**
	6 people discontinued the study with either treatment	
	1 more person discontinued the study while taking manual therapy	
Chance: Adverse effects		
NNH: n/a		
	95 people out of 100 completed either treatment because of complaints about the therapy they received.	**Not significantly significant**
	4 people out of 100 dropped out of either treatment because of complaints about the therapy they received.	
	1 more person out of 100 dropped out of manual therapy because of complaints about the therapy.	
Chance: Loss to follow-up (people who did not complete the study)		
NNH: n/a		
	79 people out of 100 completed the study with either therapy	**Not significantly significant**
	17 people out of 100 did not complete the study with either therapy	
	4 more people out of 100 did not complete the study when taking part in manual therapy	

Step 3: GRADE Evidence profile
See Table 4 a: Manual therapy program versus exercise therapy program for hip OA

Step 4: Other recommendations

Group	Recommendation
AAOS	N/A No recommendations for hip.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, *insoles*, knee bracing) and weight reduction.
OARSI	Optimal management of OA requires a combination of non-pharmacological and pharmacological modalities.

Step 5: GRADE Recommendation

References

Hoeksma HL, Dekker J, Ronday HK et al. Comparison of manual therapy and exercise therapy in osteoarthritis of the hip: a randomized clinical trial. Arthritis Rheum 2004; 51(5):722-9.

APPENDIX A: MANUAL THERAPY IN OSTEOARTHRITIS OF THE HIP: A PROTOCOL

Developed by the Department of Physical Therapy, Leyenburg Hospital and the Netherlands Institute for Health Services Research

Frequency of sessions and duration of episode

The duration of a session is 25 minutes. The frequency is twice a week at a total of 9 treatments.

Treatment protocol

Manual therapy (manipulation and stretching) is particularly aimed at the improvement of elasticity of the joint capsule and the surrounding muscles.

Muscle stretching. Muscle stretching is an integrated part of the manual therapy program. Each session starts with stretching of shortened muscles. The following muscle (groups) are stretched: m. iliopsoas, m. quadriceps femoris, m. tensor fascia latae, m. sartorius, m.m. adductors and m. gracilis (1). Starting posture is a supine position. The patient has to experience a stretching sensation. Actual stretching is applied for 8 to 10 seconds. Repeat stretching of each muscle (group) 2 times. Total time: 10–15 minutes.

Manipulation. Manipulation is performed according to a traction manipulation technique (2). The therapist's hands are placed just above the ankle joint. All manipulations are performed in slight abduction to avoid slamming of the femoral head into the acetabular surface. The first traction manipulation is performed in the maximum loosed packed position of the hip joint (2). With each following manipulation, the hip joint is placed in a more limited position (which differs per patient). In total, a maximum of 5 manipulations can be applied. The final manipulation is performed in the most limited position of the hip joint. In between manipulations, active assisted motions of the hip joint are performed for relaxation.

To evaluate the success of manipulation, after each manipulation "end feel" of the hip joint is tested using a

traction test and by passive hip flexion. This is compared with the contralateral hip. When end feel of the treated hip is similar to the contralateral hip, optimal result is concluded.

Patient education and advice. The promotion of physical activities in general is of importance. Main goal is to couple improvement in joint function with physical activities, such as walking, cycling, and swimming. Furthermore, instruction about load ability of the hip joint has to be provided.

Appendix References

1. Evjenth O, Hamberg J. Autostretching: the complete manual of specific stretching. Chattanooga (TN): Chattanooga Corp.; 1991.
2. Cyriax JH. Illustrated manual of orthopedic medicine. 2nd ed. London: Butterworth-Heinemann Medical; 1996.

APPENDIX B: EXERCISE THERAPY IN OSTEOARTHRITIS OF THE HIP: A PROTOCOL

Developed by the Department of Physical Therapy, Leyenburg Hospital and the Netherlands Institute for Health Services Research

Introduction

This is a summary of the exercise protocol. The protocol is an adaptation of the protocol of Van Baar et al (1). In addition, the book of Evjenth and Hamberg is followed on muscle stretching techniques (2). All participating physical therapists are instructed in training sessions. These training sessions will be repeated every 3 months.

Frequency of sessions and duration of episode

The duration of a session is 25 minutes. The frequency is twice a week at a total of 9 treatments.

Treatment protocol

The exercise program is tailored to the individual patient's needs by the therapist. The first session is used to compile exercise therapy treatment goals by questioning, physical examination, and observation of walking ability. It is of great importance to identify specific impairments and disabilities that are of high priority to the patient.

There are 4 main treatment goals on which exercise therapy focuses: 1) increase of muscle function, including endurance, strength, and coordination; 2) improvement of range of motion; 3) decrease of pain; and 4) improvement of walking ability. Furthermore, education and advice need to be provided to the patient.

Muscle function. Mainly active exercises have to be applied to improve muscle function. Exercises consist of muscle strengthening exercises with the use of weight or strengthening equipment. Endurance is trained by walking on a treadmill or cycling on a home trainer. Finally, coordination is trained through walking exercises with increased complexity and through balancing exercises.

Range of motion. If regarded necessary, range of joint motion can be increased through both passive and active exercises. Active exercises should have the upper hand.

Active exercises consist of 3-dimensional motions of the hip joint that go beyond the range of joint motion that most patients use in activities of daily living. These exercises can be performed in weight-bearing and non–weight-bearing positions. In addition, these exercises can be applied in different positions, such as during standing, sitting on a chair, and while lying down.

Passive exercises contain passive movement of the hip and stretching exercises according to Evjenth and Hamberg. Postures and starting positions for stretching exercises can be found in the book of Evjenth and Hamberg (2).

Pain. If regarded necessary, exercises for pain relief can be applied. Pain relief is also achieved through active joint motion exercises and through stretching exercises. In addition, second and third degree traction in the maximum loosed packed position of the hip can be applied (2).

Walking ability. Walking ability is trained by specific walking exercises with adjustment of gait pattern, use of walking aids, and instruction on climbing of stairs.

Patient education, advice, and home exercises. The promotion of exercise in general is of great importance; such activities as walking, cycling, and swimming are recommended. Concerning home management and social activities, these are specifically focused to take an active approach to pain, instead of taking rest and sitting down. Avoidance of prolonged static load and instruction on load ability of the hip should be emphasized. Instructions for home exercises, derived from the specific exercises as performed during the treatment sessions, are provided.

Appendix References

1. Van Baar ME, Assendelft WJ, Dekker J, Oostendorp RA, Bijlsma JW. The effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a randomized clinical trial. J Rheumatol 1998;25:2432–9.
2. Evjenth O, Hamberg J. Autostretching: the complete manual of specific stretching. Chattanooga (TN): Chattanooga Corp.; 1991.

4.2 Manual therapy in combination with supervised exercise and home exercise program versus home exercise program alone for knee OA

Is individualized manual therapy in combination with supervised exercise and home exercise program effective in reducing pain and improving function in patients with symptomatic knee OA compared to home exercise program? Are patients compliant to these treatment regimens?

Step 1: Search Results

There were no meta-analyses which reported the efficacy of manual therapy in patients with knee OA. A few RCTs assessed the efficacy of manual therapy specifically in patients with knee OA but most had limitations (sample size smaller than 50 participants) or used manual therapy in combination with other modalities such as taping and massage, making it difficult to evaluate its efficacy. We chose the only RCT conducted in patients with knee OA which assessed the efficacy of manual therapy in combination with supervised exercises, the treatment combination deemed the most used in clinical practice by our team of experts: Deyle (2005). We contacted the authors in order to report results for the pain and function subscales of the WOMAC since only the total WOMAC score was reported in their publication. The treatment programs used in this study are described following the results.

Intervention description: Subjects in the clinic treatment group attended 8 treatment sessions over a 4 week period in the physical therapy clinic. Manual therapy programs were individualized based on the results of the examination. The manual therapy techniques, consisting of passive physiological and accessory movements, muscle stretching, and soft tissue mobilization, were applied by the treating physical therapist primarily to the knee and surrounding structures. In addition to receiving manual therapy treatments, subjects in the clinic treatment group performed a standardized knee exercise program at each treatment session. This program consisted of active ROM exercises, muscle strengthening, muscle stretching, and riding a stationary bicycle. A physical therapist or physical therapy technician supervised these exercises. The number of strengthening exercise bouts and stationary bicycle riding time were increased or decreased by the treating physical therapist based on subject response. Subjects in the clinic treatment group performed the same home exercise program as the home exercise group each day that they were not treated in the physical therapy clinic.

Step 2: GRADE Summary of findings

Manual therapy in combination with supervised exercise and home exercise program compared to home exercise for knee OA

Patient or population: patients with knee OA
Intervention: manual therapy in combination with supervised exercise and home exercise program
Comparison: home exercise

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **Home exercise**	Corresponding risk **Manual therapy + supervised exercise and home exercise program**					
Benefits							
Pain WOMAC. Scale from: 0 to 500. Follow-up: 8 weeks	37%	53% (39% to 67%)	16%	1.43	120 (1 study[2])	⊕⊕⊕⊕ high[1]	6 (3 to 43)
Function WOMAC. Scale from: 0 to 1700. Follow-up: 8 weeks	37%	52% (38% to 66%)	15%	1.41	120 (1 study)	⊕⊕⊕⊕ high	6 (3 to 70)
Harms							
Safety				**Not reported**			
Discontinuations due to lack of adherence number of patients who discontinued due to lack of adherence to the treatment regimen (whether subjects attended all clinical appointments and reported for testing at 0, 4 and 8 weeks). Follow-up: 8 weeks	0%	0%	0%	0	120 (1 study)	⊕⊕⊕⊕ high	Not statistically significant
Withdrawals people who withdrew from the study after randomization. Follow-up: 8 weeks	12 %[3]	9% (3% to 25%)[4]	-3%	0.77 (0.28 to 2.11)	134 (1 study)	⊕⊕⊕O moderate[5]	Not statistically significant

[1] The authors report that the intention to treat results with 134 subjects did not differ substantially from the results of the 120 subjects.
[2] Another outcome reported by the author was the use of medications for OA by patients at 52 weeks. Use of medications for OA was higher in the home exercise group (68%) than the clinic treatment group (48%) and this difference was statistically significant (p=0.03).
[3] In the control group, withdrawals were due to: knee injections (1), changed medications (1), shoulder surgery (1), not willing to return (2) and moved from area (3).
[4] In the treatment group, withdrawals were due to: knee injections (2), changed medications (1), not willing to return (1), not willing to walk (1) and unrelated medical condition (1).
[5] The confidence interval ranges from not being clinically significant to a very large clinical effect, which is a sign of imprecision.

Visual Summary of Findings Table
Manual therapy in combination with supervised exercise and home exercise program compared to home exercise for knee OA

Chance: Improving pain after 8 weeks	
NNT: 6	
47 people out of 100 don't improve with either treatment	
37 people out of 100 improve with either treatment	
16 more people out of 100 improve with manual therapy in combination with a supervised exercise and home exercise program	
Chance: Improving function after 8 weeks	
NNT: 6	
48 people out of 100 don't improve with either treatment.	
37 people out of 100 improve with either treatment	
15 more people out of 100 improve with manual therapy in combination with a supervised exercise and home exercise program.	
Chance: Lack of adherence; discontinuation of therapy after 8 weeks	
NNH: n/a	**Not significantly significant**
100 people out of 100 completed either treatment	
0 people out of 100 dropped out of either treatment	
0 more people out of 100 dropped out of the manual therapy in combination with a supervised exercise and home exercise program	
Chance: Withdrawals from the trial after 8 weeks	
NNH: n/a	**Not significantly significant**
88 people out of 100 did not drop out of either treatment	
9 people out of 100 dropped out of either treatment	

☹	**3 more people** out of 100 dropped out of the home exercise program.	
Safety		
NNH: n/a		**Not reported**

Step 3: GRADE Evidence profile

See Table 4 b: Manual therapy in combination with supervised exercise and home exercise program versus home exercise program alone for knee OA

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	No recommendations for manual therapy.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, *insoles*, knee bracing) and weight reduction.
OARSI	Optimal management of OA requires a combination of non-pharmacological and pharmacological modalities.

Step 5: GRADE Recommendation

References

Deyle GD, Allison SC, Matekel RL et al. Physical therapy treatment effectiveness for osteoarthritis of the knee: a randomized comparison of supervised clinical exercise and manual therapy procedures versus a home exercise program. Phys Ther 2005;85(12):1301-17.

Description of the treatment programs:

Subjects in the clinic treatment group attended 8 treatment sessions over a 4 week period in the physical therapy clinic. Manual therapy programs were individualized based on the results of the examination. The manual therapy techniques, consisting of passive physiological and accessory movements, muscle stretching, and soft tissue mobilization, were applied by the treating physical therapist primarily to the knee and surrounding structures. In addition to receiving manual therapy treatments, subjects in the clinic treatment group performed a standardized knee exercise program at each treatment session. This program consisted of active ROM exercises, muscle strengthening, muscle stretching, and riding a stationary bicycle. A physical therapist or physical therapy technician supervised these exercises. The number of strengthening exercise bouts and stationary bicycle riding time were increased or decreased by the treating physical therapist based on subject response. Subjects in the clinic treatment group performed the

same home exercise program as the home exercise group each day that they were not treated in the physical therapy clinic.

The home exercise group received detailed verbal and hands-on instruction in a home-based program of the same exercises as the clinical treatment group. Similar to the subjects who received clinical treatment, subjects in the home exercise group were instructed that pain should be avoided in all exercises except in the case that pain or stiffness decreased with each repetition. Each subject received a detailed supporting handout containing instructions and photographs of the exercises. Subjects in the home exercise group were allowed to ride a stationary bicycle if they stated that riding a bicycle was currently part of their exercise routine or if they could not walk for safety reasons. A follow-up examination was performed for the home exercise group 2 weeks after the initial visit.

Table 1.
Comparison of Interventions by Intervention Group

Clinical Treatment Group Interventions	Performance	Home Exercise Group Interventions	Performance
Strengthening exercise	Clinic and home	Strengthening exercise	Home
Stretching exercise		Stretching exercise	
ROM exercise		ROM exercise	
Stationary bicycle[a]		Stationary bicycle[a]	
Manual therapy	Clinic	No manual therapy	
Level of exercise supervision and instruction	1 exercise instruction session 7 supervised exercise sessions	Level of exercise supervision and instruction	2 exercise instruction sessions

[a] Home stationary bicycle riding in both exercise groups was allowed if it was part of the participant's exercise program before the study. Participants in the home exercise group were not specifically instructed to ride a stationary bicycle, nor was it recorded on the exercise adherence log. ROM=range of motion.

5. PSYCHOSOCIAL INTERVENTIONS

Are psychosocial interventions effective in reducing pain and improving function in patients with symptomatic knee OA compared to usual care?

Step 1: Search Results
The chosen evidence (Dixon, 2007) constitutes the best and most recent meta-analysis found, although it pooled different psychosocial therapies without separating cognitive behavioural therapy, which constituted 70% of the interventions in the meta-analysis and did not separate patients with knee or hip OA. Other SRs were older and did not contain necessary data.

Intervention description: Program consisting of three phases: (1) education of patient; (2) skills-training in cognitive-behavioural coping skills; and (3) application to real-life situations. These are usually administered by health care professionals.

Step 2: GRADE Summary of findings

psychosocial intervention compared to no intervention for osteoarthritis of the hip and knee

Patient or population: patients with osteoarthritis of the hip and knee
Settings:
Intervention: psychosocial intervention
Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Absolute difference	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **no intervention**	Corresponding risk **psychosocial intervention**					
Benefits							
pain pooled different scales including AIMS and VAS (follow-up: 2-12 months)	41%	49% of those psychosocial intervention group experienced a decrease in pain (45% to 54%)	1.19	8%	1483 (8)	⊕⊕OO **low**[1,2]	10 (7 to 20)
Function (physical disability) (follow-up: 2-12 months)	41%	48% of those psychosocial intervention group experienced an increase in function (43% to 52)	1.17	7%	1483 (8^{2})	⊕⊕OO **low**[1,3]	12 (8 to 36)
Harms							
Safety	Not reported						
Withdrawals	Not reported						
Adherence	Not reported						

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is

likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Pooled wide range of psychosocial interventions
[2] Affected joints not described therefore could not distinguish between hip, knee, and other.
[3] No description of type of scales used.
[4] Calfas 1992, Gay 2002, Keefe 2004, Keefe 1996, Keefe 1999, Keefe 1990, Keefe 1990, Lin 2003.

Visual Summary of Findings Table
Psychosocial intervention compared to no intervention for osteoarthritis of the hip and knee

Chance: Improving pain after 2-12 months	
NNT: 10	
😐	51 people out of 100 don't improve whether or not they take part in a psychosocial intervention.
☺	41 people out of 100 improve whether or not they take part in a psychosocial intervention.
☺	**8 more people** out of 100 improve with a psychosocial intervention.
Chance: Improving function after 2-12 months	
NNT: 12	
😐	52 people out of 100 don't improve whether or not they take part in a psychosocial intervention.
☺	41 people out of 100 improve whether or not they take part in a psychosocial intervention.
☺	**7 more people** out of 100 improve with a psychosocial intervention.
Chance: Withdrawls	
The number of people who left the study was not reported.	
Chance: Safety	
Safety of psychosocial interventions was not reported.	
Chance: Adherence	
Adherence to psychosocial interventions was not reported.	

Step 3: GRADE Evidence profile
See Table 5: Psychosocial intervention compared to no intervention for OA of the hip and knee

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	We suggest patients with symptomatic OA of the knee be encouraged to participate in self-management educational programs such as those conducted by the Arthritis Foundation, and incorporate activity modifications (e.g., walking instead of running; alternative activities) into their lifestyle.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, insoles, knee bracing) and weight reduction.
OARSI	Optimal management of OA requires a combination of non-pharmacological and pharmacological modalities. 2. All patients with hip and knee OA should be given information access and education about the objectives of treatment and the importance of changes in lifestyle, exercise, pacing of activities, weight reduction, and other measures to unload the damaged joint(s). The initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health professionals. Subsequently emphasis should be placed on encouraging adherence to the regimen of non-pharmacological therapy.

Step 5: GRADE Recommendation

References

Dixon KE, Keefe FJ, Scipio CD, Perri LCM, Abernethy AP. Psychological interventions for arthritis for arthritis pain management in adults: a meta-analysis. Health Psychol 2007;26(3):241-50.

Lin EH, Katon W, Von Korff M, Tang L, Williams JW, Kroenke K et al. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. JAMA 2003;290(18):2428-9.

6. WEIGHT LOSS

Is weight loss effective in reducing pain and improving function in patients with symptomatic knee OA compared to usual care and sham acupuncture?

Step 1: Search Results
We found one meta-analysis (Christensen, 2007), which pooled the results from 4 randomized controlled trials (Christensen, 2005; Messier, 2000; Messier, 2004; Toda, 1998). Toda, 1998 results were not included in this summary of findings due to the use of pharmacological intervention to achieve weight loss. [The 8 remaining publications found were single randomized controlled trials (RCTs) and were not included. These were either already included in the meta-analysis (2), did not fall under the inclusion criteria (2) or were written in a language other than English (2). It is uncertain why 2 RCTs (Fotch 2005 and Miller 2006) were not included in the meta-analysis; it is suggested thatthese RCTs were indexed after the search performed in 2006. All of the additional RCTs findings were in the same direction as those of Christensen 2007.]

Interventions description: interventions included were weight loss interventions using CBT, nutrition, and/or exercise approaches and excluded pharmacological interventions

Step 2: GRADE Summary of findings

weight loss compared to control (no weight loss program) for knee OA

Patient or population: patients with knee osteoarthritis
Settings:
Intervention: weight loss
Comparison: control (no weight loss program)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Absolute difference	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **Control (no weight loss)**	Corresponding risk **Weight loss**					
Benefits							
pain WOMAC 500mm. Scale from: 0 to 500. (follow-up: 8-24 weeks)	36%	44% of those in weight loss group experienced a decrease in pain (37% to 52%)	1.2	7.8%	416 (2^{2})	⊕⊕⊕O **moderate**[1]	11 (not estimable)
function WOMAC 1700mm. Scale from: 0 to 1700.	34%	43% (36% to 50%)	1.26	9%	416 (2^{2})	⊕⊕⊕O **moderate**[1]	9 (5 to 52)

(follow-up: mean 8-24 weeks)	
	Harms – no harms were reported
safety	Not reported
withdrawals	Not reported
adherence	Not reported
	*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). CI: Confidence interval;
	GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.
	[1] Christensen 2005 used only low-energy diet whereas Messier 2000 used exercise and diet intervention. Length of follow-up also varied (8-24 weeks). [2] Christensen 2005, Messier 2000

Visual Summary of findings figure:
Weight loss compared to control (no weight loss program) for knee osteoarthritis

Chance: Improving pain after between 8 and 24 weeks	
NNT: 11	
😐 56 people out of 100 don't improve with or without a weight loss program	
☺ 36 people out of 100 improve with or without a weight loss program	
☺ **8 more people** out of 100 improve with participation in a weight loss program	
Chance: Improving function after between 8 and 24 weeks	
NNT: 9	
😐 57 people out of 100 don't improve with or without a weight loss program	
☺ 34 people out of 100 improve with or without participating in a weight loss program	
☺ **9 more people** out of 100 improve with participation in a weight loss program	
Chance: Harms	
Safety, adherence and the number of people who withdrew were not reported in the SR.	

Step 3: GRADE Evidence profile
See Table 6: Weight loss compared to control (no weight loss program) for knee OA

Step 4: Other recommendations

Group	Recommendation
AAOS - knee	We recommend patients with symptomatic OA of the knee, who are overweight (as defined by a BMI>25), should be encouraged to lose weight (a minimum of five percent (5%) of body weight) and maintain their weight at a lower level with an appropriate program of dietary modification and exercise.
EULAR - knee	Non-pharmacological treatment of knee OA should include regular education, exercise, appliances (sticks, insoles) and weight reduction if obese or overweight.
EULAR – hip	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, insoles, knee bracing) and weight reduction.
OARSI	All patients with hip and knee OA should be given information access and education about the objectives of treatment and the importance of changes in lifestyle, exercise, pacing of activities**, weight reduction,** and other measures to unload the damaged joint(s). The initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health professionals. Subsequently emphasis should be placed on encouraging adherence to the regimen of non-pharmacological therapy.

Step 5: GRADE Recommendation

References

Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis 2007;66(4): 433-9.

Toda Y, Toda T, Takemura S, Wada T, Morimoto T, Ogawa R. Change in body fat, but not body weight or metabolic correlates of obesity, is related to symptomatic relief of obese patients with knee osteoarthritis after a weight control program. J Rheumatol 1998; 25(11):2181–6.

Messier SP, Loeser RF, Mitchell MN, Valle G, Morgan TP, Rejeski WJ, et al. Exercise and weight loss in obese older adults with knee osteoarthritis: a preliminary study. J Am Geriatr Soc 2000;48(9):1062–72.

Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum 2004;50(5):1501–10.

Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. Osteoarthritis Cartilage 2005;13(1):20–7.

7. BRACES

7.1 Braces and medical (conservative) treatment versus medical (conservative) treatment in knee OA

Are braces and conservative treatment effective in reducing pain and improving function in patients with symptomatic uni-compartmental knee osteoarthritis (OA) and a mal-alignment compared to conservative treatment alone?

Step 1: Search Results
The most recent systematic review (SR) was the one by Brouwer, 2008 which reported one RCT conducted by the same author in 2006 and one by Kirkley in 1999. The RCT conducted by Kirkley in 1999 showed different results than the RCT by Brouwer (2006), thus we decided to display the results from both studies in the present document (section 1a and 1b).

For part 1a, we found the results reported in the SR are not the same as the ones in the Brouwer 2006 RCT so we contacted the authors. The authors mentioned that the RCT reported results stemming from an analysis which forwarded last measurements available for subjects who were lost to follow-up or for whom data were incomplete. Results in the RCT were also adjusted for baseline characteristics which were not similar. The authors recommended that we report the data from the RCT.

Intervention description: The conservative treatment was identical in both groups and consisted of standard care: i.e., patient education (adaptation of activities and/or weight loss), and (if needed) physical therapy and analgesics. In the intervention group patients were fitted with a knee brace (OAsys brace, Innovation Sports, Irvine, CA, USA); this brace is commercially available for right/left leg in four sizes. The brace consists of a thigh shell and a calf shell (both of carbon fiber) connected by titanium hinges on the medial and lateral sides. The adjustable slide bar on the medial side of the brace provides

valgisation (1 to 12.5 degrees) with medial unloading, or varisation (1 to 10 degrees) with lateral unloading. The degree of varisation or valgisation depends on the degree of malalignment and the acceptance of the patient (extensive correction will cause pressure ulcers). A specialized orthopedic technician applied the brace and gave instructions to the patients. During the follow-up this specialized orthopedic technician was present at the orthopedic outpatient department. If necessary, the brace was adjusted during the follow-up visits.

Step 2: GRADE Summary of findings

Brace and standard conservative treatment compared to standard conservative treatment only for knee OA

Patient or population: patients with knee OA
Intervention: brace and standard conservative treatment
Comparison: standard conservative treatment only

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk	Corresponding risk					
	standard conservative treatment only	**Brace and standard conservative treatment**					
Benefits							
Pain VAS. Scale from: 0 to 10. Follow-up: 6 months	38%	43% (36% to 50%)[2]	5%	1.13	117 (1 study) [1]	⊕⊕⊕O moderate [3,4]	Not statistically significant
Knee function Hospital for Special Surgery Score (HSS). Scale from: 0 to 100. Follow-up: 6 months	24%	28% (23% to 35%)[2]	4%	1.17	117 (1 study) [1]	⊕⊕⊕O moderate [3,4]	Not statistically significant
Harms							
Withdrawal from treatment due to adverse events number of patients who stopped the treatment due to adverse events Follow-up: 12 months	7%[5]	0%	-7%	8.56 (0.47 to 155.45)	117 (1 study) [1]	⊕⊕OO low [3,4,6]	Not statistically significant
Withdrawals from treatment number of patients who stopped the treatment after randomization Follow-up: 12 months	25%	42% (24% to 72%)[7]	17%	1.70 (0.98 to 2.92)	117 (1 study) [1]	⊕⊕OO low [3,4,6]	Not statistically significant
Adherence	Not reported						

[1] The SR by Brouwer (2008) reported one trial by the same authors (Brouwer, 2006).

[2] We calculated the SMD using the mean difference and confidence interval between groups with RevMan. The MD was adjusted by the authors for baseline values for age, gender, BMI, duration of complaints, severity of knee OA, pain severity, knee function, walking distance, medication and quality of life since these characteristics were not similar at baseline.
[3] The trial (Brouwer, 2006) did not blind the outcome assessors, the care providers nor the patients. Outcomes of interest were not similar at baseline.
[4] The authors of the meta-analysis conducted the present study, which may lead to a potential conflict of interest. The quality was not downgraded because of this.
[5] Adverse events include skin irritation (n=2) and bad fit (n=2).
[6] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[7] Patients stopped treatment mostly because of lack of effectiveness (n=15).

[1. a]
Visual Summary of Findings Table
Brace and standard conservative treatment compared to standard conservative treatment only for knee OA

Chance: Improving pain after 6 months		
NNT: n/a		**Not statistically significant**
😐	57 people out of 100 don't improve whether they use a brace or not.	
🙂	38 people out of 100 improve whether they use a brace or not.	
🙂	**5 more people** out of 100 improve with a brace.	
Chance: Withdrawals due to treatment after 12 months		
NNH: n/a		**Not statistically significant**
😐	93 people out of 100 did not leave the study due to adverse events whether they use a brace or not.	
☹	7 people out of 100 left the study due to adverse events whether they use a brace or not.	
☹	**No more** people out of 100 left the study when they used a brace.	
Chance: Withdrawals due to any reason after 12 months		
NNH: n/a		**Not statistically significant**
😐	58 people out of 100 did not leave the study whether they use a brace or not..	
☹	25 people out of 100 left the study whether they use a brace or not.	
☹	**17 more** people out of 100 left the study when they used a brace.	

Chance: Adherence
Adherence to using a brace was not reported.

Step 3: GRADE Evidence profile

See Table 7 a: Braces and medical (conservative) treatment versus medical (conservative) treatment

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	● We are unable to recommend for or against the use of a brace with a *valgus* directing force for patients with medial uni-compartmental OA of the knee. ● We are unable to recommend for or against the use of a brace with a *varus* directing force for patients with lateral uni-compartmental OA of the knee. ● We suggest patients with symptomatic OA of the knee use patellar taping for short term relief of pain and improvement in function.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, insoles, *knee bracing*) and weight reduction.
OARSI	In patients with knee OA and mild/moderate *varus* or *valgus* instability, a knee brace can reduce pain, improve stability and diminish the risk of falling.

Step 5: GRADE Recommendation

References

Brouwer RW, Jakma TS, Verhagen AP, Verhaar JA, Bierma-Zeinstra SM. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database of Syst Rev 2005;(1):CD004020.

Brouwer RW, van Raaij TM, Verhaar JA, Coene LN, Bierma-Zeinstra SM. Brace treatment for osteoarthritis of the knee: a prospective randomized multi-centre trial. Osteoarthritis Cartilage 2006;14(8):777.

7.2 Braces with medical (conservative) treatment versus medical (conservative) treatment alone in knee OA

Are braces in addition to medical treatment effective in reducing pain and improving function in patients with varus gonarthrosis compared to medical treatment alone?

Step 1: Search Results
Since an RCT conducted by Kirkley in 1999 showed different results than the RCT by Brouwer (2006), we decided to display the results from both studies in the present document (section 1a and 1b). The results shown in the present table were computed using the data sent to our research team by Dr. Brouwer, who had recently received it from the Kirkley Research Group but did not have time to report it in his systematic review.

Intervention description: The treatment that was provided in the medical treatment group represents the standard medical management of patients who have osteoarthritis of the knee. These patients were given an educational pamphlet on osteoarthritis, which described the pathological characteristics of the disease, how the diagnosis is determined, methods of coping, and the medical treatments available; instructions to use plain acetaminophen on an as-needed basis for relief of pain; and instructions on a home program to maintain flexibility. The regimen did not include formal physiotherapy. Patients who were taking nonsteroidal anti-inflammatory drugs at the time of presentation were asked to continue taking these medications as they had previously. All patients were asked to keep a diary about any medication that they used during the course of the trial. The patients in the unloader brace group had the same medical treatment as the control group, but they also were fitted with a Generation II valgus-producing functional knee (unloader) brace (Generation II Orthotics, Richmond, British Columbia, Canada). The brace is custom-made and consists of a polyethylene thigh shell connected to a polyethylene calf shell through a polyaxial hinge on the medial side. The hinge was

altered with use of a calibrated apparatus to allow application of a 4-degree increase in valgus in the anteroposterior plane. The patients were instructed to wear the brace while they were awake for activities that had been troublesome to them in the past and to keep a diary about their use of the brace.

Step 2: GRADE Summary of findings

Brace and medical treatment compared to medical treatment for knee OA

Patient or population: patients with knee OA
Intervention: brace and medical treatment
Comparison: medical treatment

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **Medical treatment**	Corresponding risk **brace and medical treatment**					
Benefits							
Pain WOMAC pain. Scale from: 0 to 500. Follow-up: 6 months	29%	64% (45% to 80%)[1]	35%	2.21	74 (1 study)	⊕⊕⊕O moderate[2]	3 (2 to 6)
Function WOMAC function. Scale from: 0 to 1700. Follow-up: 6 months	29%	58% (39% to 75%)[1]	29%	2	74 (1 study)	⊕⊕⊕O moderate[2]	3 (2 to 8)
Harms							
Withdrawals number of patients who withdrew from the study after randomization Follow-up: 6 months	18%	0% (0% to 19%)	-18%	0.07 (0.00 to 1.10)[3]	81 (1 study)	⊕⊕⊕O moderate[2]	Not statistically significant
Safety	Not reported						
Adherence	Not reported						

[1] The results shown in the present table were computed using the data sent to our research team by Dr. Brouwer who had recently received it from the Kirkley Research Group but did not have time to report it in his systematic review.
[2] Blinding of patients and assessors as well as intention-to-treat analyses were not mentioned in this study.
[3] We calculated this relative risk using Rev Man 5. Reasons for withdrawals include: dissatisfaction with the group to which they had been randomized (n=5), inability to attend appointments (n=2), ill health (n=1) and a change in a scheduled date for an operation (n=1).

[1. b]
Visual Summary of Findings Table
Brace and medical treatment compared to medical treatment for knee OA

Chance: Improving pain after 6 months	
NNT: 3	
😐 36 people out of 100 don't improve whether they use a brace or not.	
🙂 29 people out of 100 improve whether they use a brace or not.	
🙂 **35 more people** out of 100 improve with a brace.	
Chance: Improving function after 6 months	
NNT: 3	
😐 42 people out of 100 don't improve whether they use a brace or not.	
🙂 29 people out of 100 improve whether they use a brace or not.	
🙂 **29 more people** out of 100 improve with a brace.	
Chance: Withdrawals after 6 months	
NNH: n/a	**Not statistically significant**
😐 82 people out of 100 did not leave the study whether they use a brace or not.	
☹ 18 people out of 100 left the study whether they use a brace or not.	
☹ **No more** people out of 100 left the study when they used a brace.	
Chance: Safety	
Safety of using a brace was not reported	
Chance: Adherence	
Adherence to using a brace was not reported.	

Step 3: GRADE Evidence profile
See Table 7 b: Braces with medical (conservative) treatment versus medical (conservative) treatment alone

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	● We are unable to recommend for or against the use of a brace with a *valgus* directing force for patients with medial uni-compartmental OA of the knee. ● We are unable to recommend for or against the use of a brace with a *varus* directing force for patients with lateral uni-compartmental OA of the knee. ● We suggest patients with symptomatic OA of the knee use patellar taping for short term relief of pain and improvement in function.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, insoles, *knee bracing*) and weight reduction.
OARSI	In patients with knee OA and mild/moderate *varus* or *valgus* instability, a knee brace can reduce pain, improve stability and diminish the risk of falling.

Step 5: GRADE Recommendation

References

Kirkley A, Webster-Bogaert S, Litchfield R et al. The effect of bracing on varus gonarthrosis. J Bone Joint Surg Am 1999;81(4):539-48.

7.3 Braces and medical treatment versus neoprene sleeve with medical treatment in knee OA

Are braces in addition to medical treatment effective in reducing pain and improving function in patients with varus gonarthrosis compared to a neoprene sleeve combined with medical treatment?

Step 1: Search Results

The most recent SR on braces for knee OA was the one by Brouwer, 2008 which reported one RCT for braces versus neoprene sleeve conducted by Kirkley (1999). The results shown in the present table were computed using the data sent to our research team by Dr. Brouwer who had recently received it from the Kirkley Research Group but did not have time to report it in his systematic review.

Intervention description: Patients in the neoprene-sleeve group were directed to use the neoprene sleeve while they were awake for activities that had been troublesome to them in the past. Patients in the unloader-brace group were fitted with a Generation II valgus-producing functional knee brace. The brace is custom-made and consists of a polyethylene calf shell through a polyaxial hinge on the medial side. The hinge was altered with use of a calibrated apparatus to allow application of a 4-degree increase in valgus in the anteroposterior plane. Patients were instructed to wear the brace in the same way as the other group. The length of the treatment program was not clearly stated in the article. However, given there was a 6-month follow-up assessment, we assumed participants received treatment for that length of time.

Step 2: GRADE Summary of findings

Brace and medical treatment compared to neoprene sleeve and medical treatment for knee OA

Patient or population: patients with knee OA
Intervention: brace and medical treatment
Comparison: neoprene sleeve and medical treatment

Outcomes	Illustrative comparative risks* (95% CI)		Absolute effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk	Corresponding risk					
	neoprene sleeve and medical treatment	**brace and medical treatment**					
Benefits							
Pain WOMAC pain. Scale from: 0 to 500. Follow-up: 6 months	30%	47% (30% to 65%)[1]	17%	1.57	77 (1 study)	⊕⊕OO low[2,3]	Not statistically significant
Function WOMAC function. Scale from: 0 to 1700. Follow-up: 6 months	31%	45% (28% to 62%)[1]	14%	1.45	77 (1 study)	⊕⊕OO low[2,3]	Not statistically significant
Harms							
Withdrawals number of patients who withdrew from the study after randomization Follow-up: 6 months	5%	0% (0% to 20%)	-5%	0.19 (0.01 to 3.75)[4]	79 (1 study)	⊕⊕OO low[2,3]	Not statistically significant
Safety				Not reported			
Adherence				Not reported			

[1] The results shown in the present table were computed using the data sent to our research team by Dr. Brouwer who had recently received it from the Kirkley Research Group but did not have time to report it to his systematic review.
[2] Blinding of patients and assessors as well as intention-to-treat analyses were not mentioned in this study.
[3] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[4] We calculated this relative risk using Rev Man 5. Reasons for withdrawals for the 7 withdrawals in the control group and the 2 from the neoprene sleeve group include: dissatisfaction with the group to which they had been randomized (n=5), inability to attend appointments (n=2), ill health (n=1) and a change in a scheduled date for an operation (n=1) in the three treatment groups (brace, medical treatment and neoprene sleeve).

Step 3: GRADE Evidence profile

See Table 7 c: Braces and medical treatment versus neoprene sleeve with medical treatment

[1. c]

Visual Summary of Findings Table

Brace and medical treatment compared to neoprene sleeve and medical treatment for knee OA

Chance: Improving pain after 6 months		
NNT: 3		**Not statistically significant**
😐	53 people out of 100 don't improve with either treatment	
🙂	30 people out of 100 improve with either treatment	
🙂	**17 more people** out of 100 improve with a brace and medical treatment	
Chance: Improving function after 6 months		
NNT: 3		**Not statistically significant**
😐	55 people out of 100 don't improve with either treatment	
🙂	31 people out of 100 improve with either treatment	
🙂	**14 more people** out of 100 improve with a brace and medical treatment.	
Chance: Withdrawals after 6 months		
NNH: n/a		**Not statistically significant**
😐	95 people out of 100 did not leave the study with either treatment	
☹	5 people out of 100 left the study with either treatment.	

No more people out of 100 left the study with a brace and medical treatment	
Chance: Safety	
Safety of using a brace and medical treatment was not reported	
Chance: Adherence	
Adherence to using a brace and medical treatment was not reported.	

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	● We are unable to recommend for or against the use of a brace with a *valgus* directing force for patients with medial uni-compartmental OA of the knee. ● We are unable to recommend for or against the use of a brace with a *varus* directing force for patients with lateral uni-compartmental OA of the knee. ● We suggest patients with symptomatic OA of the knee use patellar taping for short term relief of pain and improvement in function.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, insoles, *knee bracing*) and weight reduction.
OARSI	In patients with knee OA and mild/moderate *varus* or *valgus* instability, a knee brace can reduce pain, improve stability and diminish the risk of falling.

Step 5: GRADE Recommendation

References

Kirkley A, Webster-Bogaert S, Litchfield R, Amendola A, MacDonald S, McCalden R, et al. The effect of bracing on varus gonarthrosis. J Bone Joint Surg Am 1999;81(4):539-48.

Correspondence between the Kirkley research group and Dr. Brouwer, which was sent to us by Dr. Brouwer.

8. TAPING

8.1 Medially-directed patellar taping versus no taping in knee OA

Is medially-directed patellar taping effective in reducing pain and improving function in patients with symptomatic knee OA compared to no taping?

Step 1: Search Results
We chose the most recent SR conducted by Warden 2008 which pooled results from 2 studies on patellar taping in OA patients (Hinman, 2003 and Hinman, 2003) for pain. However, only one of these trials (published in the British Medical Journal) reported function, safety, adherence and withdrawals.

Intervention description in the RCT by Hinman 2003 published in BMJ:
The trial comprised a three week intervention period and a three week follow up. Tape was applied by 12 trained physiotherapists at the university (n=4) and in private practice (n=8) around the metropolitan region. The tape was worn for three weeks and reapplied weekly. Skin was shaved before application. Therapeutic tape provided medial glide, medial tilt, and anteroposterior tilt to the patella. As inflamed soft tissue is aggravated by stretch, tape was also applied to unload either the infrapatellar fat pad or the pes anserinus (determined by clinical assessment to ascertain the most tender). Hypoallergenic undertape (Fixomull stretch; Beiersdorf, North Rhyde, NSW) was applied beneath the rigid tape (Leuko Sportstape Premium Plus; Beiersdorf) to prevent irritation of the skin. Control tape aimed to provide sensory input only. Hypoallergenic tape alone was laid over the same areas of skin as the therapeutic tape. Participants allocated to the no tape group received no intervention. All participants continued current treatments but were instructed to refrain from starting new ones.

Intervention description in the crossover study by Hinman 2003 published in Rheumatology:
Therapeutic tape was applied in a standardized manner by the same investigator, regardless of clinical presentation. Skin was shaved prior to tape application. Two pieces of rigid tape (Leuko Sportstape Premium Plus, Beiersdorf Australia Ltd) applied a medial patellar glide and corrected lateral and AP tilt. Two further pieces of tape applied distal to the patella unloaded the infrapatellar fat pad. Hypoallergenic undertape (Fixomull1 stretch, Beiersdorf Australia Ltd) was applied beneath the rigid tape to prevent skin irritation. For the neutral taping condition, hypoallergenic undertape was applied over the same areas of skin as therapeutic tape, but with no force applied to realign the patella or unload soft tissues. Participants rested for 5 min between test conditions to minimize carry-over effects of tape on cutaneous sensation. The length of time the tape was worn and the timing of the outcome assessment was not reported.

Step 2: GRADE Summary of findings

Medially-directed patellar taping compared to no taping for knee OA

Patient or population: patients with knee OA
Intervention: medially-directed patellar taping
Comparison: no taping

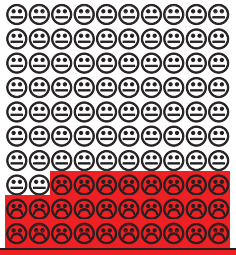
Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **No taping**	Corresponding risk **Medially-directed patellar taping**					
Benefits							
Pain[1] VAS. Scale from: 0 to 100. Follow-up: 3 weeks[2]	40%	82% (72% to 90%)[3]	42%	2.05	94 (2 studies[4])	⊕⊕OO low[5,6]	3 (2 to 3)
Function WOMAC. Scale from: 0 to 68. Follow-up: 3 weeks	37%	52% (32% to 71%)[7]	15%	1.41	58 (1 study[8])	⊕⊕OO low[9,10]	Not statistically significant
Harms							
Minor skin irritations number of subjects presenting with minor skin irritations Follow-up: 6 weeks	0%	28%	28%	17 (1.03 to 281.5)	58 (1 study[11])	⊕⊕OO low[9,10]	6 (0 to 3333) *by estimating control risk at 1%
Withdrawals number of patients who withdrew after randomization Follow-up: 6 weeks	3%	0% (0% to 27%)	-3%	0.33 (0.01 to 7.86)	58 (1 study[12])	⊕⊕OO low[9,10]	Not statistically significant
Adherence number of participants who continued to wear the tape as prescribed Follow-up: 6 weeks	100%	100%	0%	1	58 (1 study[13])	⊕⊕⊕O moderate[10]	Not statistically significant

[1] Two studies were pooled by the authors who reported a SMD (Hinman, 2003 and Hinman, 2003).
[2] One study looks at the immediate effect of taping and the other one at 3 weeks.
[3] This effect size was reported in the SR by Warden.
[4] One study was a crossover study and the other was a controlled study.
[5] According to the trials, both studies did not blind subjects and therapists who administered the treatment. However, subjects were not aware of which taping technique was considered therapeutic. Furthermore, because one of the studies (published in Rheumatology) used a crossover (within subject) design, it did not ensure proper allocation concealment and comparability of group characteristics at baseline. The quality assessment reported in the SR by Warden is not consistent with the information given in the RCTs.
[6] There is a publication bias indicated by significant funnel plot asymmetry in the SR. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.
[7] We calculated the SMD with the end of study data using RevMan.
[8] The SR did not report function. One study (Hinman, 2003 in BMJ) reported function at 3 weeks.
[9] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[10] There is a possibility of publication bias since the funnel plot showed asymmetry in the SR. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.

[11] One study (Hinman, 2003 in BMJ) reported adverse effects. Another study by the same author (Hinman, 2003 in Rheumatology) reported an absence of adverse effects.
[12] One study (Hinman, 2003 in BMJ) reported withdrawals.
[13] One study (Hinman, 2003 in BMJ) reported adherence.

Step 3: GRADE Evidence profile
See table 8 a: Medially-directed patellar taping versus no taping in knee OA

[2 a.]
Visual Summary of Findings Table
Medially-directed patellar taping compared to no taping for knee OA

Chance: Improving pain after 3 weeks		
NNT: 3		
😐	18 people out of 100 don't improve whether they applied taping or not.	
🙂	40 people out of 100 improve whether they applied taping or not.	
🙂	**42 more people** out of 100 improve with taping.	
Chance: Improving function after 3 weeks		
NNT: n/a		**Not statistically significant**
😐	48 people out of 100 don't improve whether they applied taping or not.	
🙂	37 people out of 100 improve whether they applied taping or not.	
🙂	**15 more people** out of 100 improve with taping.	
Chance: Minor skin irritation after 6 weeks		
NNH: 6		
😐	72 people out of 100 did not have minor skin irritation whether they applied taping or not	
☹	No one had a minor skin irritation whether they applied taping or not	
☹	**28 more** people out of 100 had minor skin irritation when they applied tape.	
Chance: Withdrawals after 6 weeks		

NNH: n/a		**Not statistically significant**
😐	100 people out of 100 stayed in the study whether they applied taping or not.	
☹	3 people out of 100 left the study whether they applied taping or not.	
☺	**3 fewer** people out of 100 left the study when they applied tape.	
Chance: Adherence after 6 weeks		
NNH: n/a		**Not statistically significant**
😐	0 people out of 100 did not adhere to the treatment whether they use applied taping or not.	
☹	100 people out of 100 adhered to the treatment whether they applied taping or not.	
☹	**There was no difference** in the number of people who adhered to the treatment.	

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	● We are unable to recommend for or against the use of a brace with a *valgus* directing force for patients with medial uni-compartmental OA of the knee. ● We are unable to recommend for or against the use of a brace with a *varus* directing force for patients with lateral uni-compartmental OA of the knee. ● We suggest patients with symptomatic OA of the knee use patellar taping for short term relief of pain and improvement in function.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, insoles, *knee bracing*) and weight reduction.
OARSI	In patients with knee OA and mild/moderate *varus* or *valgus* instability, a knee brace can reduce pain, improve stability and diminish the risk of falling.

Step 5: GRADE Recommendation

References

Warden SJ, Hinman RS, Watson MA, Jr., Avin KG, Bialocerkowski AE, Crossley KM. Patellar taping and bracing for the treatment of chronic knee pain: a systematic review and meta-analysis. Arthritis Rheum 2008;59(1):73-83.

Hinman RS, Crossley KM, McConnell J, Bennell KL. Efficacy of knee tape in the management of osteoarthritis of the knee: blinded randomised controlled trial. BMJ 2003;327(7407):135.

Hinman RS, Bennell KL, Crossley KM, McConnell J. Immediate effects of adhesive tape on pain and disability in individuals with knee osteoarthritis. Rheumatology (Oxford) 2003;42(7):865-9.

8.2 Medially-directed patellar taping versus sham taping in knee OA

Is medially-directed patellar taping effective in reducing pain and improving function in patients with symptomatic knee OA compared to sham taping?

Step 1: Search Results

We chose the most recent SR conducted by Warden 2008 which pooled results from 3 studies on patellar taping in OA patients (Cushnaghan, 1994, Hinman, 2003 and Hinman, 2003) for pain.

Intervention description in the RCT by Hinman 2003 published in BMJ:

The trial comprised a three week intervention period and a three week follow up. Tape was applied by 12 trained physiotherapists at the university (n=4) and in private practice (n=8) around the metropolitan region. The tape was worn for three weeks and reapplied weekly. Skin was shaved before application. Therapeutic tape provided medial glide, medial tilt, and anteroposterior tilt to the patella. As inflamed soft tissue is aggravated by stretch, tape was also applied to unload either the infrapatellar fat pad or the pes anserinus (determined by clinical assessment to ascertain the most tender). Hypoallergenic undertape (Fixomull stretch; Beiersdorf, North Rhyde, NSW) was applied beneath the rigid tape (Leuko Sportstape Premium Plus; Beiersdorf) to prevent irritation of the skin. Control tape aimed to provide sensory input only. Hypoallergenic tape alone was laid over the same areas of skin as the therapeutic tape. Participants allocated to the no tape

group received no intervention. All participants continued current treatments but were instructed to refrain from starting new ones.

Intervention description in the crossover study by Hinman 2003 published in Rheumatology:
Therapeutic tape was applied in a standardized manner by the same investigator, regardless of clinical presentation. Skin was shaved prior to tape application. Two pieces of rigid tape (Leuko Sportstape Premium Plus, Beiersdorf Australia Ltd) applied a medial patellar glide and corrected lateral and AP tilt. Two further pieces of tape applied distal to the patella unloaded the infrapatellar fat pad. Hypoallergenic undertape (Fixomull1 stretch, Beiersdorf Australia Ltd) was applied beneath the rigid tape to prevent skin irritation. For the neutral taping condition, hypoallergenic undertape was applied over the same areas of skin as therapeutic tape, but with no force applied to realign the patella or unload soft tissues. Participants rested for 5 min between test conditions to minimize carry-over effects of tape on cutaneous sensation. The length of time the tape was worn and the timing of the outcome assessment was not reported.

Intervention description of the crossover study by Cushnaghan, 1994 : The three types of taping were: neutral, in which the tape was applied directly over the front of the patella, without any pressure; medial, in which the tape pulled the patella to the medial side of the knee joint; and lateral, in which the tape was used to pull the patella to the lateral side. The taping consisted of a strip of Leukotape P (Beiersdorf, UK) applied by the same person in each case. Each tape was applied for four days, with three days of no treatment between tape positions.

Step 2: GRADE Summary of findings

Medially-directed patellar taping compared to sham taping for knee OA

Patient or population: patients with knee OA
Intervention: medially-directed patellar taping
Comparison: sham taping

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **sham taping**	Corresponding risk **medially-directed patellar taping**					
Benefits							
Pain[1] VAS. Scale from: 0 to 100. Follow-up: 3 weeks[2]	41%	68% (52% to 81%)[3]	27%	1.66	122 (3 studies[4])	⊕⊕OO low [5,6]	4 (3 to 8)
Function WOMAC. Scale from: 0 to	38%	37% (19% to 57%)	-1%	0.97	58 (1 study[7])	⊕⊕OO low [8, 9]	Not statistically significant

68. Follow-up: 3 weeks							
Harms							
Minor skin irritations number of subjects presenting with minor skin irritations Follow-up: 3 weeks	3%	27% (4% to 100%)	24%	8 (1.07 to 59.95)	58 (1 study[10])	⊕⊕OO low [8,9]	36 (1 to 476)
Adherence number of participants who continued to wear the tape as prescribed Follow-up: 6 weeks	100%	100%	0%	1	58 (1 study[11])	⊕⊕⊕O moderate [9]	Not statistically significant
Withdrawals number of participants who withdrew after randomization Follow-up: 6 weeks	0%	0%	0%	1	58 (1 study[11])	⊕⊕⊕O moderate [9]	Not statistically significant

[1] Three studies were pooled by the systematic review authors who reported a SMD (Hinman, 2003, Hinman, 2003 and Cushnagan, 1994).
[2] Studies looked at the immediate effect of taping as well as the effect after 4 days and after 3 weeks of intervention.
[3] This effect size was reported in the SR by Warden.
[4] Two were crossover studies and one was an RCT.
[5] According to the trials, all studies did not blind subjects and therapists who administered the treatment. However, subjects were not aware of which taping technique was considered therapeutic. Furthermore, because the two other studies used a crossover (within subject) design, it did not ensure proper allocation concealment and comparability of group characteristics at baseline. The quality assessment reported in the SR by Warden is not consistent with the information given in the RCTs.
[6] There is a publication bias indicated by significant funnel plot asymmetry. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.
[7] The SR did not report function. One study (Hinman, 2003 in BMJ) reported function at 3 weeks.
investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.
[8] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[9] There is a possibility of publication bias since the funnel plot showed asymmetry in the SR. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.
[10] One study (Hinman, 2003 in BMJ) reported adverse effects. The other studies reported an absence of adverse effects.
[11] One study (Hinman, 2003 in BMJ) reported adherence to the treatment regimen and withdrawals. Cushnagan also reported that all patients followed prescribe taping.

[2 b.]

Visual Summary of Findings Table
Medially-directed patellar taping compared to sham taping for knee OA

Chance: Improving pain after 3 weeks	
NNT: 4	
😐 32 people out of 100 don't improve no matter which type of taping was used.	
🙂 41 people out of 100 improve no matter which type of taping was used.	
🙂 **27 more people** out of 100 improve with medially-directed patellar taping.	
Chance: Improving function after 3 weeks	
NNT: n/a	**Not statistically significant**
😐 63 people out of 100 don't improve no matter which type of taping was used.	
🙂 37 people out of 100 improve no matter which type of taping was used.	
☹ **1 fewer person** out of 100 improve with medially-directed patellar taping.	
Chance: Minor skin irritation after 3 weeks	
NNH: 36	
😐 73 people out of 100 did not have minor skin irritation with either type of taping.	
☹ 3 people out of 100 had minor skin irritation with either type of taping.	
☹ **24 more** people out of 100 had minor skin irritation with medially-directed patellar taping.	
Chance: Adherence after 6 weeks	
NNH: n/a	**Not statistically significant**
😐 100 people out of 100 adhered to the treatment with either type of taping.	
☹ No one did not adhere to the treatment with either type of taping.	

☹	**There was no difference in the number of people** who adhered to either type of taping.	
Chance: Withdrawals		
NNH: n/a		**Not statistically significant**
😐	100 people out of 100 remained in the study with either type of taping.	
☹	No one left the study with either type of taping	
☹	**There was no difference** in the number of people who left the study with either type of taping.	

Step 3: GRADE Evidence profile

Table 8 b: Medially-directed patellar taping versus sham taping in knee OA

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	● We are unable to recommend for or against the use of a brace with a *valgus* directing force for patients with medial uni-compartmental OA of the knee. ● We are unable to recommend for or against the use of a brace with a *varus* directing force for patients with lateral uni-compartmental OA of the knee. ● We suggest patients with symptomatic OA of the knee use patellar taping for short term relief of pain and improvement in function.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, insoles, *knee bracing*) and weight reduction.
OARSI	In patients with knee OA and mild/moderate *varus* or *valgus* instability, a knee brace can reduce pain, improve stability and diminish the risk of falling.

Step 5: GRADE Recommendation

References

Warden SJ, Hinman RS, Watson MA, Jr., Avin KG, Bialocerkowski AE, Crossley KM. Patellar taping and bracing for the treatment of chronic knee pain: a systematic review and meta-analysis. Arthritis Rheum 2008;59(1):73-83.

Hinman RS, Crossley KM, McConnell J, Bennell KL. Efficacy of knee tape in the management of osteoarthritis of the knee: blinded randomised controlled trial. BMJ 2003;327(7407):135.

Hinman RS, Bennell KL, Crossley KM, McConnell J. Immediate effects of adhesive tape on pain and disability in individuals with knee osteoarthritis. Rheumatology (Oxford) 2003;42(7):865-9.

Cushnaghan J, McCarthy C, Dieppe P. Taping the patella medially: a new treatment for osteoarthritis of the knee joint? BMJ 1994;308:753–5.

8.3 Laterally-directed patellar taping versus medially-directed patellar taping in knee OA

Is laterally-directed patellar taping effective in reducing pain and improving function in patients with symptomatic knee OA compared to medially-directed patellar taping?

Step 1: Search Results

We chose the most recent SR conducted by Warden 2008 which reported one study comparing lateral to medial patellar taping in OA patients for pain (Cushnaghan, 1994).

Intervention description: The three types of taping in the Cushnaghan study were: neutral, in which the tape was applied directly over the front of the patella, without any pressure; medial, in which the tape pulled the patella to the medial side of the knee joint; and lateral, in which the tape was used to pull the patella to the lateral side. The taping consisted of a strip of Leukotape P (Beiersdorf, UK) applied by the same person in each case. Each tape was applied for four days, with three days of no treatment between tape positions.

Step 2: GRADE Summary of findings

Laterally-directed patellar taping compared to medially-directed patellar taping for knee OA

Patient or population: patients with knee OA
Intervention: laterally-directed patellar taping
Comparison: medially-directed patellar taping

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **medially-directed patellar taping**	Corresponding risk **laterally-directed patellar taping**					
Benefits							
Pain VAS. Scale from: 0 to 100. Follow-up: 4 days		*Not estimable due to lack of data	SMD 0.95 (0.42 to 1.48) [1]	*	28 (1 study[2])	⊕⊕◯◯ low [3,4]	*
Function	Not reported						
Harms							
Safety number of patients who reported adverse events follow-up: 4 days	0%	0%	0%	1	28 (1 study[2])	⊕⊕◯◯ low [3,4]	Not statistically significant
Adherence number of patients who wore tapes on for the full four days follow-up: 4 days	100%	100%	0%	1	28 (1 study[2])	⊕⊕◯◯ low [3,4]	Not statistically significant
Withdrawals number of patients who withdrew after entry to the study follow-up: 4 days	0%	0%	0%	1	28 (1 study[2])	⊕⊕◯◯ low [3,4]	Not statistically significant

[1] The SR by Warden reported an SMD for pain comparing lateral and medial taping based on the Cushnagan, 1994 study.
[2] This study has a crossover design with 14 participants.
[3] This study did not blind therapists who administered the treatment and it is unclear if patients were blinded. However, subjects were not aware of which taping technique was considered therapeutic. Also, because this study used a crossover (within subject) design, it did not ensure proper allocation concealment and comparability of group characteristics at baseline.
[4] There is a possibility of publication bias since the funnel plot showed asymmetry in the SR. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.

[2 c.]
Visual Summary of Findings Table
Laterally-directed patellar taping compared to medially-directed patellar taping for knee OA

Chance: Improving pain after 4 days		
The improvement in pain was not estimable due to lack of data.		
Chance: Improving function after 4 days		
The improvement in function was not reported.		
Chance: Safety		
NNH: n/a		**Not statistically significant**
😐	100 people out of 100 did not have adverse events with either type of taping	
☹	No one had adverse events with either type of taping	
☹	**There was no difference** in the safety of the two types of taping.	
Chance: Adherence after 4 days		
NNH: n/a		**Not statistically significant**
😐	100 people out of 100 adhered to either type of taping	
☹	No one did not adhere to the treatment with either type of taping	
☹	**There was no difference** in the number of people who adhered to either type of taping**.**	
Chance: Withdrawals after 4 days		
NNH: n/a		**Not statistically significant**
😐	100 people out of 100 remained in the study with either type of taping.	
☹	No one left the study with either type of taping	
☹	**There was no difference** in the number of people who left the study with either type of taping.	

Step 3: GRADE Evidence profile
See Table 8c: Laterally-directed patellar taping versus medially-directed patellar taping in knee OA

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	● We are unable to recommend for or against the use of a brace with a *valgus* directing force for patients with medial uni-compartmental OA of the knee. ● We are unable to recommend for or against the use of a brace with a *varus* directing force for patients with lateral uni-compartmental OA of the knee. ● We suggest patients with symptomatic OA of the knee use patellar taping for short term relief of pain and improvement in function.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, insoles, *knee bracing*) and weight reduction.
OARSI	In patients with knee OA and mild/moderate *varus* or *valgus* instability, a knee brace can reduce pain, improve stability and diminish the risk of falling.

Step 5: GRADE Recommendation

References

Warden SJ, Hinman RS, Watson MA, Jr., Avin KG, Bialocerkowski AE, Crossley KM. Patellar taping and bracing for the treatment of chronic knee pain: a systematic review and meta-analysis. Arthritis Rheum 2008;59(1):73-83.

Cushnaghan J, McCarthy C, Dieppe P. Taping the patella medially: a new treatment for osteoarthritis of the knee joint? BMJ 1994;308:753–5.

8.4 Laterally-directed patellar taping versus neutral sham taping in knee OA

Is laterally-directed patellar taping effective in reducing pain and improving function in patients with symptomatic knee OA compared to sham taping?

Step 1: Search Results
We chose the most recent SR conducted by Warden 2008 which reported one study comparing lateral patellar taping to neutral sham taping in OA patients for pain (Cushnaghan, 1994).

Intervention description: The three types of taping in the Cushnaghan study were: neutral, in which the tape was applied directly over the front of the patella, without any pressure; medial, in which the tape pulled the patella to the medial side of the knee joint; and lateral, in which the tape was used to pull the patella to the lateral side. The taping consisted of a strip of Leukotape P (Beiersdorf, UK) applied by the same person in each case. Each tape was applied for four days, with three days of no treatment between tape positions.

Step 2: GRADE Summary of findings

Laterally-directed patellar taping compared to neutral sham taping for knee OA

Patient or population: patients with knee OA
Intervention: laterally-directed patellar taping
Comparison: neutral sham taping

Outcomes	Illustrative comparative risks* (95% CI)		Absolute difference	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT
	Assumed risk **neutral sham taping**	Corresponding risk **laterally-directed patellar taping**					
Benefits							
Pain[1] VAS. Scale from: 0 to 100. Follow-up: 4 days	35%	33% (17% to 54%)	-2%	0.94	28 (1 study[2])	⊕OOO very low[3,4,5]	Not statistically significant
Function	Not reported						
Harms							
Safety number of patients who reported adverse events	0%	0%	0%	1	28 (1 study[2])	⊕⊕OO low[3,5]	Not statistically significant

follow-up: 4 days							
Adherence number of patients who wore tapes on for the full four days follow-up: 4 days	100%	100%	0%	1	28 (1 study[2])	⊕⊕OO low [3,5]	Not statistically significant
Withdrawals number of patients who withdrew after entry to the study follow-up: 4 days	0%	0%	0%	1	28 (1 study[2])	⊕⊕OO low [3,4]	Not statistically significant

[1] The SR by Warden reported an SMD for pain comparing lateral and neutral taping based on the Cushnagan, 1994 study.
[2] This study has a crossover design with 14 participants.
[3] This study did not blind therapists who administered the treatment and it is unclear if patients were blinded. Also, because this study used a crossover (within subject) design, it did not ensure proper allocation concealment and comparability of group characteristics at baseline.
[4] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[5] There is a possibility of publication bias since the funnel plot showed asymmetry in the SR. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.

[2 d.]
Visual Summary of Findings Table
Laterally-directed patellar taping compared to neutral sham taping for knee OA

Chance: Improving pain after 4 days		
NNT: n/a		**Not statistically significant**
😐	67 people out of 100 don't improve with either type of taping	
☺	33 people out of 100 improve with either type of taping	
☹	**2 fewer people** out of 100 improve with laterally-directed patellar taping**.**	
Chance: Improving function after 4 days		
The improvement in function was not reported.		
Chance: Safety after 4 days		
NNH: n/a		**Not statistically significant**
😐	100 people out of 100 did not report adverse effects with either type of taping.	
☹	0 people out of 100 reported adverse effects with either type of taping	
☹	**There was no difference** in the safety of the two types of taping.	
Chance: Adherence after 4 days		
NNH: n/a		

😐	100 people out of 100 adhered to the treatment with either type of taping	**Not statistically significant**
☹	0 people out of 100 did not adhere to the treatment with either type of taping	
☹	**There was no difference** in the number of people who adhered to either type of taping.	
Chance: Withdrawals after 4 days		
NNH: n/a		**Not statistically significant**
😐	100 people out of 100 remained in the study with either type of taping.	
☹	No one left the study with either type of taping	
☹	**There was no difference** in the number of people who left the study with either type of taping.	

Step 3: GRADE Evidence profile
See Table 8 d: Laterally-directed patellar taping versus neutral sham taping in knee OA

Step 4: Other recommendations

Group	Recommendation
AAOS (knee)	● We are unable to recommend for or against the use of a brace with a *valgus* directing force for patients with medial uni-compartmental OA of the knee. ● We are unable to recommend for or against the use of a brace with a *varus* directing force for patients with lateral uni-compartmental OA of the knee. ● We suggest patients with symptomatic OA of the knee use patellar taping for short term relief of pain and improvement in function.
EULAR	Non-pharmacological treatment of knee OA should include education, exercise, appliances (sticks, insoles, *knee bracing*) and weight reduction.
OARSI	In patients with knee OA and mild/moderate *varus* or *valgus* instability, a knee brace can reduce pain, improve stability and diminish the risk of falling.

Step 5: GRADE Recommendation

References

Warden SJ, Hinman RS, Watson MA, Jr., Avin KG, Bialocerkowski AE, Crossley KM. Patellar taping and bracing for the treatment of chronic knee pain: a systematic review and meta-analysis. Arthritis Rheum 2008;59(1):73-83.

Cushnaghan J, McCarthy C, Dieppe P. Taping the patella medially: a new treatment for osteoarthritis of the knee joint? BMJ 1994;308:753–5.

ABBREVIATIONS

OA - osteoarthritis

RCT – randomized controlled trial

SR – SR

GRADE evidence profiles

Table 1 a: Home-based balance exercises versus home-based strengthening exercises for knee OA

Author(s): Karine Toupin April
Date: 2009-06-12
Question: Should balance training versus strength training be used for knee OA?
Bibliography: Chaipinyo, 2009

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	balance training	strength training	Relative (95% CI)	Absolute	Quality	Importance
pain (follow-up 4 weeks; measured with: Knee injury and Osteoarthritis Outcome Score (KOOS); range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	None	24	18	0.73	SMD -0.23 (-0.85 to 0.38)[4]	⊕⊕OO LOW	CRITICAL
function in daily living (follow-up 4 weeks; measured with: Knee injury and Osteoarthritis Outcome Score (KOOS); range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	None	24	18	0.54	SMD -0.45 (-1.07 to 0.17)[4]	⊕⊕OO LOW	CRITICAL
Adherence (follow-up 4 weeks; Maximum number of days:28; measured with: average number of days of exercise performed by participants Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	None	24	18	-	MD 2 (-0.77 to 4.77)	⊕⊕OO LOW	CRITICAL
Withdrawals												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	None	0/24 0%	6/24 (25%)	0.08 (0.00 to 1.29)	23 fewer per 100 (from 25 fewer to 7 more)[5]	⊕⊕OO LOW	CRITICAL
Safety												
Not reported												

[1] The physiotherapists prescribing the exercises were not blinded to group allocation. We did not downgrade the quality assessment score for this. However, the number of patients in this trial is small (n=42), which could undermine its validity.
[2] Participants were volunteers from the community 50 years and older. We did not downgrade the quality assessment score for this.
[3] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[4] The authors report the mean difference over time between groups but it does not coincide with our results using Rev Man 5 because the authors did not report the level of accuracy needed (no decimals reported). We calculated the SMD using Rev Man 5.
[5] Withdrawals were due to other illnesses, personal reasons or impossibility to reach patients.

Table 1 b: Balance exercises in addition to strengthening exercises versus strengthening exercises alone for knee OA

Author(s): Karine Toupin April
Date: 2009-06-12
Question: Should kinesthesia and balance exercises in addition to strengthening exercises versus strengthening exercises be used for knee OA?
Bibliography: Diracoglu, 2005

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	kinesthesia and balance exercises in addition to strength exercises	strength exercises	Relative (95% CI)	Absolute	Quality	Importance
physical function (follow-up 8 weeks; measured with: WOMAC; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	No serious inconsistency	no serious indirectness[2]	Serious[3]	None	30	30	1.55	SMD 0.46 lower (0.97 lower to 0.05 higher)[4]	⊕⊕OO LOW	CRITICAL
Pain												
No evidence available[5]												
Adverse effects (follow-up 8 weeks; number of patients with event)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	0/30 (0%)	0/30 (0%)	1	0 more per 100	⊕⊕⊕O MODERATE	CRITICAL
Adherence (follow-up 8 weeks; Maximum number of visits:24; mean number of missed visits)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24	24	-	MD -2	⊕⊕⊕O MODERATE	CRITICAL
Withdrawals (follow-up 8 weeks; number of patients who withdrew after randomization)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/33 (9.1%)	3/33 (9.1%)	1 (0.22 to 4.6)	0 fewer per 100 (from 7 fewer to 33 more)[6]	⊕⊕⊕O MODERATE	CRITICAL

[1] The randomization method used is the "one-to-one" method which allocates one patient to the study group and the other patient to the control group one by one according to their order of application to the outpatient clinic. This method could lead to biases. Furthermore, blinding was not reported and intention to treat analyses were not performed.
[2] All patients included in the study were women 35 to 65 years old. We did not downgrade the quality of the study because of this.
[3] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[4] The authors reported the end of study results in both groups, which showed a statistically significant difference. However, their results did not coincide with our results from Rev Man 5 because the authors did not report the level of accuracy needed.
[5] Pain was not measured in the RCT. However, the use of paracetamol was reported, which could represent a proxy measure for pain to some extent. The authors report that 5 patients used paracetamol during the study in a dosage of less than 500 mg daily. The 2 groups were not significantly different from each other regarding paracetamol use (P > 0.05).
[6] Patients withdrew because of the difficulty to come to the clinic for exercises.

Table 1 c: Cardiovascular land-based exercise versus usual care for knee OA

Author(s): Jessie McGowan, Maria Benkhalti
Date: 2009-07-23
Question: Should cardiovascular land exercise versus no exercise be used for osteoarthritis of the knee?
Settings:
Bibliography:

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	cardiovascular land exercise	no exercise	Relative (95% CI)	Absolute		
pain (measured with: pooled studies with different scales including WOMAC and VAS amongst others; range of scores: 0-0; Better indicated by less)												
4[1]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	225	126	1.71	SMD -0.48 (-0.83 to -0.13)	⊕⊕⊕⊕ HIGH	CRITICAL
function (measured with: pooled studies with different scales including WOMAC and VAS amongst others; range of scores: 0-0; Better indicated by less)												
3[4]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	208	109	1.55	SMD -0.35 (-0.58 to -0.11)	⊕⊕⊕⊕ HIGH	CRITICAL
withdrawals (follow-up mean 18 months; number of withdrawals)												
1[5]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[6]	none	27/144 (18.8%)	22/149 (14.8%)	RR 1.27 (0.76 to 2.12)	40 more per 1000 (from 36 fewer to 166 more)	⊕⊕⊕O MODERATE	CRITICAL
Safety (follow-up mean 18 months; number of falls)												
1[5]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/144 (1.4%)	0/149 (0%)	RR 5.17 (0.25 to 106.82)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
adherence (follow-up mean 18 months; numbers of patients)												
1[5]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	98/144 (68.1%)	142/149 (95.3%)	RR 0.71 (0.63 to 0.80)	276 fewer per 1000 (from 191 fewer to 353 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Minor 1989, Ettinger 1997, Bautch 1997, Talbot 2003
[2] Evidence mostly included participants with early or mild symptomatic disease.
[4] Minor 1989, Ettinger 1997, Bautch 1997
[5] Ettinger 1997
[6] Is imprecise; includes no effect and significant benefit (0.76, 2.12)

Table 1 d: Resistance land-based exercise versus usual care for knee OA

Author(s): Jessie McGowan, Maria Benkhalti
Date: 2009-07-23
Question: Should resistance land exercise versus no exercise be used for osteoarthritis of the knee?
Settings:
Bibliography:

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	resistance land exercise	no exercise	Relative (95% CI)	Absolute	Quality	Importance
Pain (measured with: pooled studies with different scales including WOMAC and VAS amongst others; Better indicated by less)												
9	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness[1]	No serious imprecision	none	836	547	1.66	SMD -0.53 (-0.79 to -0.27)	⊕⊕⊕⊕ HIGH	CRITICAL
Function (measured with: pooled studies with different scales including WOMAC and VAS amongst others; Better indicated by less)												
9[2]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness[1]	No serious imprecision	none	836	547	2.5	SMD -0.58 (-0.88 to -0.27)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Evidence mostly included participants with early or mild symptomatic disease.
[2] Schilke 2006, Ettinger 1997, Baker 2001, Thomas 2002, Gur 2002, Huang 2003, Huang 2005, Thorstensson 2005, Mikesky 2006

Table 1 e: Aquatic exercise versus no exercise for OA of hip or knee

Author(s): Jessie McGowan, Maria Benkhalti
Date: 2009-08-18
Question: Should aquatic exercise versus no exercise be used for osteoarthritis of hip or knee?
Settings:
Bibliography:

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	aquatic exercise	no exercise	Relative (95% CI)	Absolute	Quality	Importance
Pain after intervention (measured with: Pooled different scales[1]; range of scores: -; Better indicated by less)												
4[2]	randomised trial	no serious limitations[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	306	332	1.2	SMD -0.19 (-0.04 to -0.35)	⊕⊕⊕⊕ HIGH	CRITICAL
Pain follow up (follow-up mean 18 months; measured with: WOMAC pain ; range of scores: 0-20; Better indicated by less)												
1[4]	randomised trial	no serious limitations[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	152	158	1.1	SMD -0.11 (-0.33 to 0.12)[5]	⊕⊕⊕⊕ HIGH	CRITICAL
Function after intervention (measured with: Pooled different scales[1]; range of scores: -; Better indicated by less)												
4[2]	randomised trial	no serious limitations[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	314	334	1.3	SMD -0.26 (-0.11 to -0.42)	⊕⊕⊕⊕ HIGH	CRITICAL
Function follow up (follow-up mean 18 months; measured with: WOMAC physical function; range of scores: 0-68; Better indicated by less)												
1[4]	randomised trial	no serious limitations[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	150	156	1.1	SMD -0.1 (-0.33 to 0.12)	⊕⊕⊕⊕ HIGH	CRITICAL
Withdrawals follow up (follow-up mean 18 months; total withdrawals)												
1[4]	randomised trial	no serious limitations[3]	no serious inconsistency	no serious indirectness	Serious[7]	none	53/153 (34.6%)	46/159 (28.9%)	RR 1.2 (0.86 to 1.66)	58 more per 1,000	⊕⊕⊕ MODERATE	IMPORTANT

[1] Pooled different scales including WOMAC, VAS, HAQ
[2] Cochrane 2005, Foley 2003, Wang 2004, Patrick 2001
[3] Patients not blinded to treatment as it is impossible to do so, therefore we did not downgrade
[4] Cochrane 2005
[5] This RCT had a significant SMD immediately after intervention
[7] 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm

Table 1 f: Aquatic exercise versus land-based exercise for knee OA

Author(s): Jessie McGowan, Maria Benkhalti
Date: 2009-07-23
Question: Should aquatic exercise versus land exercise be used for osteoarthritis of the knee?
Settings:
Bibliography:

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	aquatic exercise	land exercise	Relative (95% CI)	Absolute		
pain (follow-up mean 6 weeks; measured with: VAS; range of scores: 0-10; Better indicated by less)												
1[1]	randomised trial	serious[2]	no serious inconsistency	no serious indirectness[3]	very serious[4]	none	23	23	2.0	SMD -0.86 (-1.47 to -0.25)	⊕OOO VERY LOW	CRITICAL
function - walking ability (follow-up mean 6 weeks; measured with: timed 1-mile walk; range of scores: -; Better indicated by less)												
1[1]	randomised trial	no serious limitations[2]	no serious inconsistency	serious[3]	very serious[4]	none	23	23	1.9	SMD -0.43 (-1.01 to 0.16)	⊕OOO VERY LOW	CRITICAL

[1] Wyatt 2001
[2] Concealment of allocation was unclear
[3] no comparison to placebo
[4] N is low (n=42) and large CI (upper or lower confidence limit crosses an effect size of 0.5 in either direction)

Table 1 g: Tai Chi compared to no exercise (education on OA) for knee OA

Author(s): Jessie McGowan, Maria Benkhalti
Date: 2009-07-23
Question: Should tai chi versus no exercise (education on OA) be used for osteoarthritis of the knee?
Settings:
Bibliography:

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Tai Chi	no exercise (education on OA)	Relative (95% CI)	Absolute	Quality	
Pain (follow-up mean 12 weeks; measured with: WOMAC; range of scores: 0-35; Better indicated by less)												
1[1]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	none	18	13	1.1	SMD 0.06 (-0.65 to 0.77)	⊕⊕OO LOW	CRITICAL
Function (follow-up mean 12 weeks; measured with: WOMAC; range of scores: 0-85; Better indicated by less)												
1[1]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	none	18	13	1.1	SMD 0.07 (-0.65 to 0.78)	⊕⊕OO LOW	CRITICAL
Withdrawals (follow-up mean 12 weeks; Number of drop-outs)												
1[1]	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	Very serious[2]	none	4/22 (18.2%)	6/19 (31.6%)	RR 0.58 (0.19 to 1.74)	133 fewer per 1,000	⊕⊕OO LOW	IMPORTANT

[1] Brismee, 2007
[2] Imprecise because RR crosses no effect and significant benefit (for withdrawals)and small N=31

Table 1 h: Exercise compared to no exercise for osteoarthritis of the hip

Author(s): Jessie McGowan, Maria Benkhalti
Date: 2009-07-23
Question: Should exercise versus no exercise be used for osteoarthritis of the hip?
Settings:
Bibliography:

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	exercise	no exercise	Relative (95% CI)	Absolute		
pain (follow-up 3-18 months; measured with: pooled WOMAC ; range of scores: 0-100; Better indicated by less)												
7[1]	randomised trial	no serious limitations	No serious indirectness	Serious[2]	no serious imprecision	none	158	152	1.6	SMD -0.58 (-0.81 to -0.35)	⊕⊕⊕O MODERATE	CRITICAL

[1] Fransen 2007, Rooks 2006, Cochrane 2005, Tak 2005, Foley 2003, Hopman-Rock 2000, Van Baar 1998.
[2] although Isquared = 0, different interventions pooled, including aquatic, tai chi, and land exercise.

Table 2 a: Laterally wedged insoles versus neutrally wedged insoles for knee OA

Author(s): Jessie McGowan, Maria Benkhalti, Karine Toupin April
Date: 2009-04-28
Question: Should Laterally wedged insoles versus neutrally wedged insoles be used for painful medial Knee OA?
Bibliography: Brouwer, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Laterally wedged insoles	neutrally wedged insoles	Relative (95% CI)	Absolute		
Pain (follow-up 6 months; measured with: WOMAC; range of scores: 0-100; Better indicated by less)												
1	randomised trial	serious[1]	No serious inconsistency	no serious indirectness	Serious[2]	None	78	69	0.71	SMD 0.31 (-0.01 to 0.64)[3]	⊕⊕OO LOW	CRITICAL
Physical function (follow-up mean 6 months; measured with: WOMAC; range of scores: 0-100; Better indicated by less)												
1	randomised trial	serious[1]	No serious inconsistency	no serious indirectness	Serious[2]	None	78	69	0.71	SMD 0.30 (-0.03 to 0.62)[4]	⊕⊕OO LOW	CRITICAL
Adherence (follow-up 6 months; number of patients who wore insoles permanently during the study period)												
1	randomised trial	serious[1]	No serious inconsistency	no serious indirectness	no serious imprecision	None	72/82 (87.8%)	55/74 (74.3%)	1.18 (1.01 to 1.38)	13 more per 100 (from 1 more to 28 more)	⊕⊕⊕O MODERATE	CRITICAL
Withdrawals due to intolerance to the treatment (follow-up 6 months; number of patients who withdrew from the study because of intolerance to the treatment)												
1	Randomized trial	serious[1]	No serious inconsistency	no serious indirectness	Serious[2]	None	0/82 (0%)	1/74 (1.4%)	0.30 (0.01 to 7.28)	1 more per 100 (from 1 more to 8 more)	⊕⊕OO LOW	CRITICAL

[1] The randomization procedure and allocation concealment were not described. The trial (Maillefert, 2001) did not blind the outcome assessors and the care providers. The insoles were individually modeled and therefore the intervention was not identical for all patients. The quality assessment score was not reduced because of this.
[2] The confidence interval ranges from not being clinically significant to a very large clinical effect, which shows imprecision.
[3] This SMD was calculated using RevMan 5 with the 6-month end of study data. WOMAC pain was more decreased in the neutrally wedged group than the laterally wedged group. This result along with those at 1, 3, 12 and 24 months is not statistically significant.
[4] This SMD was calculated using RevMan 5 with the 6-month end of study data. WOMAC function was more decreased in the laterally wedged group than the neutrally wedged group. This result along with those at 1, 3, 12 and 24 months is not statistically significant.

Table 2 b: Medial wedged insoles versus neutrally wedged insoles for knee OA

Author(s): Karine Toupin April
Date: 2009-05-01
Question: Should Medially wedged insoles versus neutrally wedged insoles be used for knee OA?
Bibliography: Rodrigues 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Medially wedged insoles	neutrally wedged insoles	Relative (95% CI)	Absolute	Quality	
Pain on movement (follow-up 8 weeks; measured with: VAS scale transformed into percentage of change over time; range of scores: 0-100; Better indicated by lower values)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	16	14	2.07	SMD -1.25 (-2.04 to -0.46)[2]	⊕⊕⊕O MODERATE	CRITICAL
Function (follow-up 8 weeks; measured with: WOMAC transformed into percentage of change over time; range of scores: 0-100; Better indicated by lower values)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	16	14	3.19	SMD -1.70 (-2.55 to 0.84)[2]	⊕⊕⊕O MODERATE	CRITICAL
Mild discomfort (follow-up 8 weeks; number of patients with event)												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	None	0/16 (0%)	1/14 (7.1%)	0.29 (0.01 to 6.69)	5 fewer per 100 (from 7 fewer to 41 fewer)	⊕⊕OO LOW	IMPORTANT
Adherence												
All patients used the insoles regularly throughout the study												
Withdrawals												
No withdrawals												

[1] The sample is small: 30 women with valgus knee OA. Pain at rest was statistically different at baseline.
[2] This SMD was calculated using RevMan 5 with the percentage of change over time provided by the authors.
[3] The confidence interval ranges from not being clinically significant to a very large clinical effect, which shows imprecision.

Table 2 c: Subtalar strapped insoles versus inserted laterally wedged insoles for knee OA

Author(s): Karine Toupin April
Date: 2009-05-02
Question: Should Subtalar strapped insoles versus inserted laterally wedged insoles be used for knee OA?
Bibliography: Brouwer 2008

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Subtalar strapped insoles	inserted laterally wedged insoles	Relative (95% CI)	Absolute	Quality	Importance
Pain (follow-up 6 months; measured with: visual analog scale; range of scores: 0-100; Better indicated by lower values)												
1	Randomized trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	29	32	1.61	SMD -0.57 (-1.09 to -0.06)[2]	⊕⊕⊕O MODERATE	CRITICAL
Function (follow-up 6 months; measured with: Lequesne index; range of scores: 0-24; Better indicated by lower values)												
1	Randomized trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	29	32	1.30	SMD -0.27 (-0.78 to 0.23)[3]	⊕⊕⊕O MODERATE	CRITICAL
Side effects (follow-up 8 weeks; number of patients with event)												
1	Randomized trial	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	None	6/46 (13%)	1/44 (2.3%)	5.74 (0.72 to 45.77)	11 more per 100 (from 1 fewer to 102 more)[5]	⊕⊕OO LOW	CRITICAL
Withdrawals												
1	Randomized trial	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	None	3/32 (9.4%)	2/34 (5.9%)	1.59 (0.28 to 8.93)	3 more per 100 (from 4 fewer to 47 more)[6]	⊕⊕OO LOW	CRITICAL
Adherence												
Not reported												

[1] The randomization procedure was done according to birth date and the allocation concealment was not described. The trials (Toda, 2001, 2004 and 2006) did not blind the outcome assessors, the care providers or the patients.
[2] This SMD was calculated using Rev Man 5 with the 6-months end of study data. This result along with the one at 8 weeks are statistically significant (SMD= -0.42 (-0.83, 0)). The data at 24 month were not statistically significant.
[3] This SMD was calculated using Rev Man 5 with the 6-months end of study data. This result along with the one at 8 weeks and 24 months are not statistically significant.
[4] The confidence interval ranges from not being clinically significant to a very large clinical effect, which is a sign of imprecision.

[5] In the strapped insole group, 3 participants complained of popliteal pain, 2 reported low back pain and one had foot sole pain. Only one patient complained of foot sole pain in the inserted insole group. However, side effects were not severe enough to deter participants from continuing to wear the insole.
[6] People who withdrew had either moved or cited household commitments.

Table 3: Self-management programs for knee OA

Author(s): Jessie McGowan, Maria Benkhalti
Date: 2009-08-12
Question: Should Self-management program versus no self-management be used for knee osteoarthritis?
Bibliography: Chodosh, 2005

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management program	no self-management	Relative (95% CI)	Absolute	Quality	Importance
pain (follow-up 2-6 months; measured with: Not specified but likely pooled several different scales; range of scores: -; Better indicated by less)												
14[1]	randomised trial	no serious limitations	no serious inconsistency	very serious[2]	no serious imprecision	None	0[3]	0[3]	-	SMD -0.06 (-0.1 to -0.02)	⊕⊕OO LOW	CRITICAL
function (follow-up 2-6 months; measured with: Not specified but likely pooled several different scales; range of scores: -; Better indicated by less)												
12[4]	randomised trial	no serious limitations	no serious inconsistency	very serious[2]	no serious imprecision	None	0[3]	0[3]	-	SMD -0.06 (-0.1 to -0.02)	⊕⊕OO LOW	CRITICAL

[1] Barlow 2000, Blixen 2004, Edworth and Devins 1999, Goeppinger 1989, Hopman-Rock and Westhoff 2000, Hughes 2004, Keefe 1990, Lorig 1999, Lorig 1986, Lorig 1985, Lorig 1989, Messier 2004, Ravaud 2004, Solomon 2002
[2] This review had a very broad definition of self-management program and could not identify specific elements significantly associated with greater efficacy of self-management programs. Also, no specification of affected joints (knee, hip, or other)
[3] Total number of participants was not provided
[4] Barlow 2000, Blixen 2004, Edworthy and Devins 1999, Goeppinger 1989, Hughes 2004, Keefe 1990, Lorig 1999, Lorig 1986, Lorig 1985, Lorig 1989, Ravaud 2004, Solomon 2002

Table 4 a: Manual therapy program versus exercise therapy program for hip OA

Author(s): Karine Toupin April
Date: 2009-08-07
Question: Should manual therapy versus exercise therapy be used for hip OA?
Bibliography: Hoeksma 2004

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	manual therapy	exercise therapy	Relative (95% CI)	Absolute	Quality	
pain at rest (follow-up 5 weeks; measured with: visual analog scale; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	53	50	1.54	SMD -0.47 (-0.86 to -0.08)[3]	⊕⊕⊕⊕ HIGH	CRITICAL
physical function (follow-up 5 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	None	53	50	1.11	SMD 0.10 (-0.28 to 0.49)[3]	⊕⊕⊕O MODERATE	CRITICAL
pain at rest (follow-up 29 weeks; measured with: visual analog scale; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	None	45	44	1.25	SMD -0.26 (-0.68 to 0.15)[4]	⊕⊕⊕O MODERATE	CRITICAL
physical function (follow-up 29 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	None	44	44	1.29	SMD 0.25 (-0.17 to 0.67)[4]	⊕⊕⊕O MODERATE	CRITICAL
Adherence (follow-up 5 weeks; number of patients who prematurely discontinued the treatment programs)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	None	4/56 (7.1%)	3/53 (5.7%)	1.26 (0.30 to 5.37)	1 more per 100 (from 4 fewer to 25 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects (number of patients who discontinued the treatment programs because of increase of complaints)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	None	3/56 (5.4%)	2/53 (3.8%)	1.42 (0.25 to 8.16)	2 more per 100 (from 3 fewer to 27 more)[5]	⊕⊕⊕O MODERATE	CRITICAL
Losses to follow-up (follow-up 29 weeks; number of patients who were lost to follow-up)												
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	None	12/56 (21.4%)	9/53 (17%)	1.26 (0.58 to 2.75)	4 more per 100 (from 7 fewer to 30 more)[5]	⊕⊕⊕O MODERATE	CRITICAL

[1] This trial was a single-blind study. The authors mention that it was not possible to blind either patients or therapists for the allocated treatment. Therefore, extra attention was given to the blinding of the outcome assessor. A placebo effect may also be present in this study due to the nature of the interventions. Finally, a limitation of the study is the relatively large number of patients who received total hip arthroplasty during the follow-up period. However, no significant differences were found between the conclusions based on the intention-to-treat analysis and the per-protocol analysis. The quality of the study was not downgraded because of these reasons.

[2] The confidence interval ranges from not being clinically significant to a very large clinical effect, which is a sign of imprecision.
[3] This SMD was calculated with RevMan 5 with the end-of-study data at the end of the treatment period (5-weeks).
[4] This SMD was calculated with RevMan 5 with the end-of-study data at 29 weeks of follow-up.
[5] In the exercise program, one patient also discontinued treatment because of cardio-respiratory disease.

Table 4 b: Manual therapy in combination with supervised exercise and home exercise program versus home exercise program alone for knee OA

Author(s): Karine Toupin April
Date: 2009-08-19
Question: Should manual therapy in combination with supervised exercise and home exercise program vs home exercise be used for knee OA?
Bibliography: Deyle, 2005

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Manual therapy+ supervised exercise and home exercise program	Home exercise	Relative (95% CI)	Absolute	Quality	Importance
pain (follow-up 8 weeks; measured with: WOMAC; range of scores: 0-500; Better indicated by lower values)												
1[1]	randomised trials	no serious limitations[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	60	1.43	SMD -0.41 (-0.77 to -0.05)	⊕⊕⊕⊕ HIGH	CRITICAL
function (follow-up 8 weeks; measured with: WOMAC; range of scores: 0-1700; Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	60	1.41	SMD -0.40 (-0.76 to -0.03)	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinuations due to lack of adherence (follow-up 8 weeks; number of patients who were discontinued to lack of adherence to the treatment regimen)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/60 (0%)	0/60 (0%)	0 (0 to 0)	0 fewer per 100 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Withdrawals (follow-up 8 weeks; people who withdrew from the study after randomization)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	6/66 (9.1%)[4]	8/68 (11.8%)[5]	RR 0.77 (0.28 to 2.11)	3 fewer per 100 (from 8 fewer to 13 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Another outcome reported by the author was the use of medications for OA by patients at 52 weeks. Use of medications for OA was higher in the home exercise group (68%) than the clinic treatment group (48%) and this difference was statistically significant (p=0.03).
[2] The authors report that the intention to treat results with 134 subjects did not differ substantially from the results of the 120 subjects.
[3] The confidence interval ranges from not being clinically significant to a very large clinical effect, which is a sign of imprecision.
[4] In the treatment group, withdrawals were due to: knee injections (2), changed medications (1), not willing to return (1), not willing to walk (1) and unrelated medical condition (1).
[5] In the control group, withdrawals were due to: knee injections (1), changed medications (1), shoulder surgery (1), not willing to return (2) and moved from area (3).

Table 5: Psychosocial intervention compared to no intervention for OA of the hip and knee

Author(s): Jessie McGowan, Maria Benkhalti
Date: 2009-07-23
Question: Should psychosocial intervention vs no intervention be used for osteoarthritis of the hip and knee?
Settings:
Bibliography:

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	psychosocial intervention	no intervention	Relative (95% CI)	Absolute		
pain (follow-up 2-12 months; measured with: pooled different scales including AIMS and VAS; range of scores: 0-0; Better indicated by less)												
8	randomised trial	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	783[3]	700	1.19	SMD -0.22 (-0.11 to -0.33)	⊕⊕OO LOW	CRITICAL
function (physical disability) (follow-up 2-12 months; range of scores: 0-0; Better indicated by less)												
8[4]	randomised trial	serious[1]	no serious inconsistency	serious[5]	no serious imprecision	none	783	700	1.17	SMD 0.18 (0.06 to 0.29)	⊕⊕OO LOW	CRITICAL

[1] Pooled wide range of psychosocial interventions
[2] Affected joints not described therefore could not distinguish between hip, knee, and other.
[3] Data obtained from Dixon 2007 supplement (appendix 5)
[4] Calfas 1992, Gay 2002, Keefe 2004, Keefe 1996, Keefe 1999, Keefe 1990, Keefe 1990, Lin 2003.
[5] No description of type of scales used.

Table 6: Weight loss compared to control (no weight loss program) for knee OA

Author(s): Jessie McGowan, Maria Benkhalti
Date: 2009-04-28
Question: Should weight loss versus control (no weight loss program) be used for knee OA?
Bibliography: Christensen, 2007

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	weight loss	control (no weight loss)	Relative (95% CI)	Absolute	Quality	Importance
pain (follow-up 8-24 weeks; measured with: pooled WOMAC 500mm; range of scores: 0-500 and Likert; range of scores 1-5; Better indicated by less)												
2[1]	randomised trial	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	none	208	208	1.2	SMD -0.2 (-0.39 to 0)	⊕⊕⊕O MODERATE	CRITICAL
function (follow-up mean 8-24 weeks; measured with: pooled WOMAC 1700mm; range of scores: 0-1700 and self-reported disability; range of scores 23-115 ; Better indicated by less)												
2[1]	randomised trial	no serious limitations	serious[2]	no serious indirectness	no serious imprecision	none	208	208	1.3	SMD -0.23 (-0.42 to -0.04)	⊕⊕⊕O MODERATE	CRITICAL

[1] Christensen 2005, Messier 2000
[2] Christensen 2005 used only low-energy diet whereas Messier 2000 used exercise and diet intervention. Length of follow-up also varied (8-24 weeks).

Table 7 a: Braces and medical (conservative) treatment versus medical (conservative) treatment knee OA

Author(s): Jessie McGowan, Karine Toupin April
Date: 2009-05-21
Question: Should Brace and standard conservative treatment versus standard conservative treatment only be used for knee OA?
Bibliography: Brouwer,2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Brace and standard conservative treatment	standard conservative treatment only	Relative (95% CI)	Absolute	Quality	
Pain (follow-up 6 months; measured with: VAS; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none[2]	60	57	1.13	SMD -0.12 (-0.30 to 0.06)[3]	⊕⊕⊕O MODERATE	CRITICAL
Knee function (follow-up 6 months; measured with: HSS; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None[2]	60	57	1.03	SMD 0.15 (-0.16 to 0.20)[3]	⊕⊕⊕O MODERATE	CRITICAL
Withdrawal from treatment due to adverse events (follow-up 12 months; number of patients who stopped the treatment because of adverse events)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	Serious[4]	none[2]	4/60 (6.7%)[5]	0/57 (0%)	8.56 (0.47 to 155.45)	0 more per 100 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Withdrawals from treatment (follow-up 12 months; number of patients who stopped the treatment after randomization)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[4]	None[2]	25/60 (41.7%)[6]	14/57 (24.6%)	1.70 (0.98 to 2.92)	17 more per 100 (from 0 fewer to 47 more)	⊕⊕OO LOW	CRITICAL
Adherence												
Not reported												

[1] The trial (Brouwer, 2006) did not blind the outcome assessors, the care providers nor the patients. Outcomes of interest were not similar at baseline.
[2] The authors of the meta-analysis conducted the present study, which may lead to a potential conflict of interest. The quality was not downgraded because of this.
[3] We calculated the SMD using the mean difference and confidence interval between groups with RevMan. The MD was adjusted by the authors for baseline values for age, gender, BMI, duration of complaints, severity of knee OA, pain severity, knee function, walking distance, medication and quality of life since these characteristics were not similar at baseline.
[4] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[5] Adverse events include skin irritation (n=2) and bad fit (n=2).
[6] Patients stopped treatment mostly because of lack of effectiveness (n=15).

Table 7 b: Braces and medical (conservative) treatment versus medical (conservative) treatment alone in knee OA

Author(s): Karine Toupin April
Date: 2009-09-14
Question: Should brace and medical treatment versus medical treatment be used for knee OA?
Bibliography: Kirkley 1999

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	brace and medical treatment	medical treatment	Relative (95% CI)	Absolute	Quality	Importance
pain (follow-up 6 months; measured with: WOMAC pain; range of scores: 0-500; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	No serious imprecision	None	41	33	2.21	SMD -0.89 (-1.38 to -0.41)[2]	⊕⊕⊕O MODERATE	CRITICAL
function (follow-up 6 months; measured with: WOMAC function; range of scores: 0-1700; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	No serious imprecision	None	41	33	2	SMD -0.76 (-1.23 to -0.28)[2]	⊕⊕⊕O MODERATE	CRITICAL
withdrawals (follow-up 6 months; number of patients who withdrew from the study after randomization)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	No serious imprecision	None	0/41 (0%)	7/40 (17.5%)	0.07 (0.00 to 1.10)[3]	16 fewer per 100 (from 17 fewer to 2 more)	⊕⊕⊕O MODERATE	CRITICAL
Safety												
Not reported												
Adherence												
Not reported												

[1] Blinding of patients and assessors as well as intention-to-treat analyses were not mentioned in this study.
[2] The results shown in the present table were computed using the data sent to our research team by Dr. Brouwer who had recently received it from the Kirkley Research Group but did not have time to report it to his systematic review.
[3] We calculated this relative risk using Rev Man 5. Reasons for withdrawals include: dissatisfaction with the group to which they had been randomized (n=5), inability to attend appointments (n=2), ill health (n=1) and a change in a scheduled date for an operation (n=1).

Table 7 c: Braces and medical treatment versus neoprene sleeve with medical treatment in knee OA

Author(s): Karine Toupin Aprl
Date: 2009-09-14
Question: Should brace and medical treatment versus neoprene sleeve and medical treatment be used for knee OA?
Bibliography: Kirkley, 1999

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	brace and medical treatment	neoprene sleeve and medical treatment	Relative (95% CI)	Absolute	Quality	Importance
Pain (follow-up 6 months; measured with: WOMAC pain; range of scores: 0-500; Better indicated by lower values)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	None	41	36	1.57	SMD -0.44 (-0.89 to 0.01)[3]	⊕⊕OO LOW	CRITICAL
function (follow-up 6 months; measured with: WOMAC function; range of scores: 0-1700; Better indicated by lower values)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	None	41	36	1.45	SMD -0.35 (-0.80 to 0.10)[3]	⊕⊕OO LOW	CRITICAL
withdrawals (follow-up 6 months; number of patients who withdrew from the study after randomization)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	None	0/41 (0%)	2/38 (5.3%)	0.19 (0.01 to 3.75)[4]	4 fewer per 100 (from 5 fewer to 14 more)	⊕⊕OO LOW	CRITICAL
Safety												
Not reported												
Adherence												
Not reported												

[1] Blinding of patients and assessors as well as intention-to-treat analyses were not mentioned in this study.
[2] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[3] The results shown in the present table were computed using the data sent to our research team by Dr. Brouwer who had recently received it from the Kirkley Research Group but did not have time to report it to his systematic review. The SMDs were computed using the change in outcomes over time.
[4] We calculated this relative risk using Rev Man 5. Reasons for withdrawals the 7 withdrawals in the control group and the 2 from the neoprene sleeve group include: dissatisfaction with the group to which they had been randomized (n=5), inability to attend appointments (n=2), ill health (n=1) and a change in a scheduled date for an operation (n=1) in the three treatment groups (brace, medical treatment and neoprene sleeve).

Table 8 a: Medially-directed patellar taping versus no taping in knee OA

Author(s): Karine Toupin April
Date: 2009-06-16
Question: Should medially-directed patellar taping versus no taping be used for knee OA?
Bibliography: Warden, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	medially-directed patellar taping	no taping	Relative (95% CI)	Absolute	Quality	
pain (follow-up 3 weeks[1]; measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
2	randomised trials[2]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	47	47[5]	2.05	SMD -1.17 (-1.51 to -0.83)[6]	⊕⊕OO LOW	CRITICAL
function (follow-up 3 weeks; measured with: WOMAC; range of scores: 0-68; Better indicated by lower values)												
1[7]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[9]	29	29	1.41	SMD -0.37 (-0.89 to 0.15)[10]	⊕⊕OO LOW	CRITICAL
minor skin irritations (follow-up 6 weeks; number of subjects presenting with minor skin irritations)												
1[11]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[9]	8/29 (27.6%)	0/29 (0%)	17 (1.03 to 281.5)	0 more per 100 (from 0 more to 0 more)	⊕⊕OO LOW	CRITICAL
withdrawals (follow-up 6 weeks; number of patients who withdrew after randomization)												
1[12]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[9]	0/29 (0%)	1/29 (3.4%)	0.33 (0.01 to 7.86)	2 fewer per 100 (from 3 fewer to 24 more)	⊕⊕OO LOW	CRITICAL
Adherence (follow-up 6 weeks; number of participants who continued to wear the tape as prescribed)												
1[13]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[9]	29/29 (100%)	29/29 (100%)	1	0 fewer per 100 (from 100 fewer to 100 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] One study looks at the immediate effect of taping and the other one at 3 weeks.
[2] One study was a crossover study and the other was a controlled study.
[3] According to the trials, both studies did not blind subjects and therapists who administered the treatment. However, subjects were not aware of which taping technique was considered therapeutic. Furthermore, because one of the studies (published in Rheumatology) used a crossover (within subject) design, it did not ensure proper allocation concealment and comparability of group characteristics at baseline. The quality assessment reported in the SR by Warden is not consistent with the information given in the RCTs.
[4] There is a publication bias indicated by significant funnel plot asymmetry in the SR. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.
[5] The study in BMJ included 29 in each group and the crossover study in Rheumatology included 18 patients who had both medially-directed taping and no taping.
[6] This effect size was reported in the SR by Warden.
[7] The SR did not report function. One study (Hinman, 2003 in BMJ) reported function at 3 weeks.
[8] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[9] There is a possibility of publication bias since the funnel plot showed asymmetry in the SR. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.
[10] We calculated the SMD with the end of study data using RevMan.
[11] One study (Hinman, 2003 in BMJ) reported adverse effects. Another study by the same author (Hinman, 2003 in Rheumatology) reported an absence of adverse effects.

[12] One study (Hinman, 2003 in BMJ) reported withdrawals.
[13] One study (Hinman, 2003 in BMJ) reported adherence.

Table 8 b: Medially-directed patellar taping versus sham taping in knee OA

Author(s): Karine Toupin April
Date: 2009-09-16
Question: Should medially-directed patellar taping versus sham taping be used for knee OA?
Bibliography: Warden, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	medially-directed patellar taping	sham taping	Relative (95% CI)	Absolute	Quality	
pain (follow-up 3 weeks[1]; measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
3	randomised trials[2]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	61	61[5]	1.66	SMD -0.69 (-1.11 to -0.28)[6]	⊕⊕OO LOW	CRITICAL
function (follow-up 3 weeks; measured with: WOMAC; range of scores: 0-68; Better indicated by lower values)												
1[7]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	Serious[8]	reporting bias[9]	29	29	0.97	SMD 0.04 (-0.47 to 0.56)	⊕⊕OO LOW	CRITICAL
minor skin irritations (follow-up 3 weeks; number of subjects presenting with minor skin irritations)												
1[10]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	Serious[8]	Reporting bias[9]	8/29 (27.6%)	1/29 (3.4%)	8 (1.07 to 59.95)	24 more per 100 (from 0 more to 203 more)	⊕⊕OO LOW	CRITICAL
adherence (follow-up 6 weeks; number of participants who continued to wear the tape as prescribed)												
1[11]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	Reporting bias[9]	29/29 (100%)	29/29 (100%)	1	0 fewer per 100 (from 100 fewer to 100 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Withdrawals												
1[11]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	Reporting bias[9]	0/29 (0%)	0/29 (0%)	1	0 fewer per 100 (from 100 fewer to 100 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] Studies looked at the immediate effect of taping as well as the effect after 4 days and after 3 weeks of intervention.
[2] Two were crossover studies and one was an RCT.
[3] According to the trials, studies did not blind subjects (though it is unclear in the Cushnagan study if patients were blinded) and therapists who administered the treatment. However, subjects were not aware of which taping technique was considered therapeutic. Furthermore, because the two other studies used a crossover (within subject) design, it did not ensure proper allocation concealment and comparability of group characteristics at baseline. The quality assessment reported in the SR by Warden is not consistent with the information given in the RCTs.
[4] There is a publication bias indicated by significant funnel plot asymmetry. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.
[5] The study published by Hinman in BMJ included 29 in each group, the study by the same author in Rheumatology included 18 patients and the study by Cushnagan included 14 patients.

[6] This effect size was reported in the SR by Warden.
[7] The SR did not report function. One study (Hinman, 2003 in BMJ) reported function at 3 weeks.
[8] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[9] There is a possibility of publication bias since the funnel plot showed asymmetry in the SR. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.
[10] One study (Hinman, 2003 in BMJ) reported adverse effects. The other studies reported an absence of adverse effects.
[11] One study (Hinman, 2003 in BMJ) reported adherence to the treatment regimen. Cushnagan also reported that all patients followed prescribe taping.

Table 8 c: Laterally-directed patellar taping versus medially-directed patellar taping in knee OA

Author(s): Karine Toupin April
Date: 2009-09-16
Question: Should laterally-directed patellar taping versus medially-directed patellar taping be used for knee OA?
Bibliography: Warden, 2008

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	laterally-directed patellar taping	medially-directed patellar taping	Relative (95% CI)	Absolute	Quality	Importance
Pain (follow-up 4 days; measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials[1]	Serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	14	14[5]	*Not estimable due to lack of data	SMD 0.95 (0.42 to 1.48)[4]	⊕⊕OO LOW	CRITICAL
Function												
Not reported												
Safety (follow-up 4 days; number of patients who reported adverse events)												
1	randomised trials[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	Reporting bias[3]	0/14 (0%)	0/14[5] (0%)	1	0 fewer per 100	⊕⊕OO LOW	CRITICAL
Adherence (follow-up 4 days; number of patients who wore tapes on for the full four days)												
1	randomised trials[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	Reporting bias[3]	14/14 (0%)	14/14[5] (0%)	1	0 fewer per 100	⊕⊕OO LOW	CRITICAL
Withdrawals												
1	randomised trials[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	Reporting bias[3]	0/14 (0%)	0/14[5] (0%)	1	0 fewer per 100	⊕⊕OO LOW	CRITICAL

[1] This study by Cushnaghan has a crossover design with 14 patients.
[2] This study did not blind therapists who administered the treatment and it is unclear if patients were blinded. However, subjects were not aware of which taping technique was considered therapeutic. Also, because this study used a crossover (within subject) design, it did not ensure proper allocation concealment and comparability of group characteristics at baseline.
[3] There is a possibility of publication bias since the funnel plot showed asymmetry in the SR. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.
[4] This effect size was reported in the SR by Warden.
[5] 14 patients received all three types of taping (medial, lateral and neutral) at different time points.

Table 8 d: Laterally-directed patellar taping versus neutral sham taping in knee OA

Author(s): Karine Toupin April
Date: 2009-09-16
Question: Should laterally-directed patellar taping versus neutral sham taping be used for knee OA?
Bibliography: Warden, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	laterally-directed patellar taping	neutral sham taping	Relative (95% CI)	Absolute	Quality	
Pain (follow-up 4 days; measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials[1]	Serious[2]	no serious inconsistency	no serious indirectness	serious[3]	Reporting bias[4]	14	14[5]	0.94	SMD 0.05 (-0.48 to 0.57)[6]	⊕OOO VERY LOW	CRITICAL
Function												
Not reported												
Safety (follow-up 4 days; number of patients who reported adverse events)												
1	randomised trials[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	Reporting bias[4]	0/14 (0%)	0/14[5] (0%)	1	0 fewer per 100	⊕⊕OO LOW	CRITICAL
Adherence (follow-up 4 days; number of patients who wore tapes on for the full four days)												
1	randomised trials[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	Reporting bias[4]	14/14 (0%)	14/14[5](0%)	1	0 fewer per 100	⊕⊕OO LOW	CRITICAL
Withdrawals												
1	randomised trials[1]	Serious[2]	no serious inconsistency	no serious indirectness	No serious imprecision	Reporting bias[4]	0/14 (0%)	0/14[5](0%)	1	0 fewer per 100	⊕⊕OO LOW	CRITICAL

[1] This study by Cushnaghan has a crossover design with 14 participants.
[2] This study did not blind therapists who administered the treatment and it is unclear if patients were blinded. However, subjects were not aware of which taping technique was considered therapeutic. Also, because this study used a crossover (within subject) design, it did not ensure proper allocation concealment and comparability of group characteristics at baseline. Finally, intention to treat was not performed.
[3] The confidence interval ranges from not being clinically significant to a large clinical effect, which shows imprecision.
[4] There is a possibility of publication bias since the funnel plot showed asymmetry in the SR. This asymmetry indicates that negative studies investigating patellar taping are less likely to be published and smaller studies are more likely to produce larger effect sizes.
[5] 14 patients received all three types of taping (medial, lateral and neutral) at different time points.
[6] This effect size was reported in the SR by Warden.

Surgery

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Arthritis Care & Research
Vol. 74, No. 9, September 2022, pp 1399–1408
DOI 10.1002/acr.24893
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2022 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty

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Objective. To develop updated guidelines for the perioperative management of disease-modifying medications for patients with rheumatic diseases, specifically those with inflammatory arthritis (IA) and those with systemic lupus erythematosus (SLE), undergoing elective total hip arthroplasty (THA) or elective total knee arthroplasty (TKA).

Methods. We convened a panel of rheumatologists, orthopedic surgeons, and infectious disease specialists, updated the systematic literature review, and included currently available medications for the clinically relevant population, intervention, comparator, and outcomes (PICO) questions. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and the strength of recommendations using a group consensus process.

Results. This guideline updates the 2017 recommendations for perioperative use of disease-modifying antirheumatic therapy, including traditional disease-modifying antirheumatic drugs, biologic agents, targeted synthetic small-molecule drugs, and glucocorticoids used for adults with rheumatic diseases, specifically for the treatment of patients with IA, including rheumatoid arthritis and spondyloarthritis, those with juvenile idiopathic arthritis, or those with SLE who are undergoing elective THA or TKA. It updates recommendations regarding when to continue, when to withhold, and when to restart these medications and the optimal perioperative dosing of glucocorticoids.

Conclusion. This updated guideline includes recently introduced immunosuppressive medications to help decision-making by clinicians and patients regarding perioperative disease-modifying medication management for patients with IA and SLE at the time of elective THA or TKA.

INTRODUCTION

Advances in antirheumatic therapy have led to remarkable improvements in treatment and quality of life for people with rheumatic musculoskeletal diseases (RMDs); however, total hip arthroplasty (THA) and total knee arthroplasty (TKA) remain a mainstay of treatment among RMD patients with advanced symptomatic joint damage, most frequently those with inflammatory arthritis (IA), including spondylarthritis (SpA), rheumatoid arthritis (RA), or psoriatic arthritis (PsA), and those with systemic lupus erythematosus (SLE) (1–7). THA and TKA are successful procedures that improve mobility and decrease pain for people with RMD and end-stage arthritis. However, the risk of superficial and deep periprosthetic joint infection (PJI), a devastating complication, is increased after surgery in people with RMD, and avoiding infection is a top priority for them: patients with RA have a 50% increased risk of PJI compared to those with osteoarthritis (8,9). A panel of patients with RA was convened in 2017 prior to the publication of the American College of Rheumatology/American Association of Hip and Knee Surgeons (ACR/AAHKS) perioperative guideline and clearly stated that any risk of infection, while rare, was much more significant to them than the possibility of a postoperative flare, despite flares reported in >60% of patients after surgery (8,10–12). Recommendations regarding perioperative management of antirheumatic medications in the 2017 ACR/AAHKS guideline need updating to include drugs introduced in the interim, as well as review of more recent relevant publications.

The optimal strategy for perioperative medication management remains unknown, but antirheumatic therapy is a readily modifiable risk factor for infection, whereas other risk factors for adverse outcomes, including disease activity or severity or long-term glucocorticoid (GC) use, may not be modifiable (13–15). The ACR systematically updates guidelines every 5 years; therefore, to update the 2017 perioperative medication management guideline, the ACR and AAHKS convened a panel of rheumatologists, orthopedic surgeons, and infectious disease specialists and conducted a systematic review of the new literature published since the last guideline, adding new medications to those previously available, although direct applicable evidence remains sparse in the literature. This guideline applies to management of antirheumatic medication for adult patients with IA, including those with RA, SpA, PsA, or ankylosing spondylitis (AS), adults with juvenile idiopathic arthritis (JIA), and adult patients with SLE undergoing elective THA or TKA.

Given the increased infection risk seen in patients with IA and patients with SLE undergoing these procedures, the existing evidence base used to guide our recommendations, the time afforded by these elective procedures to manage medications, and the frequent use of these procedures in patients with IA or SLE (4,6,16), we have restricted our recommendations to those undergoing either THA or TKA. A guideline cannot address all clinical situations and scenarios but seeks to provide recommendations for commonly encountered clinical problems.

While the principles surrounding these recommendations may be extrapolated and applied to other surgical procedures, it should be noted that the evidence and consensus used to inform this guideline were drawn primarily from orthopedic literature. As in the prior version, this guideline does not address indications for THA or TKA, medical decisions unrelated to antirheumatic drug therapy, the choice of the implant, the surgical approach, or the perioperative evaluation and management of concurrent disease, such as that affecting the cervical spine of patients with RA. Although routine perioperative care and preoperative optimization for patients with RA, SpA, JIA, or SLE include assessing risk of venous thromboembolism and major acute coronary events (17,18), this guideline does not address cardiac risk assessment or perioperative venous thromboembolism prophylaxis, as both are covered in existing guidelines (19–22). The goal of this updated guideline is to provide optimal support for clinicians and patients making decisions regarding medication management at the time of elective THA or TKA surgery.

METHODS

This guideline was developed following the ACR guideline development process and in accordance with ACR policies guiding

The article is published simultaneously in *Arthritis & Rheumatology* and *Journal of Arthroplasty*.

Supported by the American College of Rheumatology and the American Association of Hip and Knee Surgeons.

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr.24893&file=acr24893-sup-0001-Disclosureform.pdf.

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Submitted for publication February 9, 2022; accepted in revised form April 7, 2022.

Table 1. Populations included in this guideline*

Adults age ≥18 years diagnosed with RA, SpA, including AS and PsA, JIA, or SLE who are deemed to be appropriate surgical candidates, are undergoing elective THA or TKA, and who are receiving antirheumatic drug therapy at the time of surgery
All patients carrying the above diagnoses without restriction to those meeting classification criteria
SLE includes patients with severe or not severe SLE, defined as follows
Severe SLE: currently treated (induction or maintenance) for severe organ manifestations: lupus nephritis, CNS lupus, severe hemolytic anemia (hemoglobin <9.9 gm/dl), platelets <50,000, vasculitis (other than mild cutaneous vasculitis), including pulmonary hemorrhage, myocarditis, lupus pneumonitis, severe myositis (with muscle weakness, not just high enzymes), lupus enteritis (vasculitis), lupus pancreatitis, cholecystitis, lupus hepatitis, protein-losing enteropathy, malabsorption, orbital inflammation/myositis, severe keratitis, posterior severe uveitis/retinal vasculitis, severe scleritis, optic neuritis, anterior ischemic optic neuropathy (derived from the SELENA–SLEDAI flare index and the BILAG 2004 index)
Not severe SLE: not currently treated for above manifestations

* RA = rheumatoid arthritis; SpA = spondyloarthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis; SLE = systemic lupus erythematosus; THA = total hip arthroplasty; TKA = total knee arthroplasty; CNS = central nervous system; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; BILAG = British Isles Lupus Assessment Group.

management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), which includes Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology and a framework for developing and presenting evidence (23,24) and adheres to Appraisal of Guidelines for Research and Evaluation (AGREE) criteria (25). The process for updating the 2017 guidelines began in 2021 (26). The populations included in this guideline are defined in Table 1 and are unchanged. Table 2 contains a list of the included drugs, along with their dosing intervals (reflecting the duration of effect), with the drugs newly added for this 2022 update denoted with footnotes. Brand names were used for newer medications that are likely to be unfamiliar to some orthopedists. Supplementary Appendix 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24893, includes a detailed description of the methods. Briefly, 3 teams were formed: a Core Leadership Team, a Literature Review Team, and a Voting Panel. The Core Leadership Team (SMG, BDS, AY, and JAS) confirmed that the population, intervention, comparator, and outcomes (PICO) questions would be the same as the ones used for the 2017 guideline, with updated medication lists to include any therapies approved for use in the US as of August 26, 2021, the stop date of our literature review (see Table 2 for medication list and Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24893, for the PICO list, including outcomes; see Supplementary Appendices 3 and 4, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24893, for the search strategies and study selection process, respectively).

The Literature Review Team performed updates of the systematic literature review for each PICO, graded the quality of evidence (high, moderate, low, very low), and produced the evidence report (see Supplementary Appendix 5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24893). The systematic literature review was updated by searching for relevant published literature from March 6, 2016 to August 26, 2021, because the previous systematic literature review for the 2017 guideline was performed from January 1, 1980 through March 6, 2016. Although the updated literature review added to the evidence report, the overall quality of the evidence remained low due to indirect evidence or small numbers of included cases. Because the overall quality of evidence was low, we included a review of the background risk for adverse events associated with THA or TKA in patients with RA, SpA, JIA, or SLE that is independent of use of the medications of interest to give context to our deliberations. Severe SLE is defined in Table 1 and refers to those patients with severe organ manifestations such as nephritis. We did not repeat our search for additional indirect evidence regarding medication risks associated with our drugs of interest; included medications are listed in Table 2.

The Voting Panel included 2 patients who have undergone arthroplasty surgery and who participated in the 2017 guideline's Patient Panel, one of whom participated in the previous Voting Panel. The panel reviewed evidence summaries from both the 2017 project and this update and discussed and voted on recommendation statements. The recommendation regarding anifrolumab and voclosporin was voted on via email. A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. Consensus required ≥70% agreement on both direction (for or against) and strength (strong or conditional) for each recommendation. Per GRADE methodology, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when the decision is more sensitive to individual patient preferences, or when costs are expected to impact the decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision-making.

Rosters of the Core Leadership Team, Literature Review Team, and Voting Panel are included in Supplementary Appendix 6, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24893. This study did not involve human subjects, and therefore, approval from Human Studies Committees was not required.

Table 2. Medications included in this 2022 guideline update*

	Dosing interval	Recommended timing of surgery since last medication dose
Medications to continue through surgery		
DMARDs: continue these medications through surgery (all patients)		
Methotrexate	Weekly	Anytime
Sulfasalazine	Once or twice daily	Anytime
Hydroxychloroquine	Once or twice daily	Anytime
Leflunomide (Arava)	Daily	Anytime
Doxycycline	Daily	Anytime
Apremilast (Otezla)	Twice daily†	Anytime†
Severe SLE-specific medications: continue these medications in the perioperative period in consultation with the treating rheumatologist‡		
Mycophenolate mofetil	Twice daily	Anytime
Azathioprine	Daily or twice daily	Anytime
Cyclosporine	Twice daily	Anytime
Tacrolimus	Twice daily (IV and PO)	Anytime
Rituximab (Rituxan)	IV every 4–6 months†	Month 4–6†
Belimumab SC (Benlysta)	Weekly†	Anytime†
Belimumab IV (Benlysta)	Monthly†	Week 4†
Anifrolumab (Saphnelo)§	IV every 4 weeks†	Week 4†
Voclosporin (Lupkynis)§	Twice daily†	Continue†
Medications to withhold prior to surgery¶		
Biologics: withhold these medications through surgery		
Infliximab (Remicade)	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Adalimumab (Humira)	Every 2 weeks	Week 3
Etanercept (Enbrel)	Every week	Week 2
Golimumab (Simponi)**	Every 4 weeks (SQ) or every 8 weeks (IV)	Week 5 Week 9
Abatacept (Orencia)	Monthly (IV) or weekly (SC)	Week 5; week 2
Certolizumab (Cimzia)	Every 2 or 4 weeks	Week 3 or 5
Rituximab (Rituxan)	2 doses 2 weeks apart every 4–6 months	Month 7
Tocilizumab (Actemra)	Every week (SC) or every 4 weeks (IV)	Week 2; week 5
Anakinra (Kineret)	Daily	Day 2
IL-17 secukinumab (Cosentyx)	Every 4 weeks	Week 5
Ustekinumab (Stelara)	Every 12 weeks	Week 13
Ixekizumab (Taltz)§	Every 4 weeks†	Week 5†
IL-23 guselkumab (Tremfya)§	Every 8 weeks†	Week 9†
JAK inhibitors: withhold this medication 3 days prior to surgery#		
Tofacitinib (Xeljanz)	Daily or twice daily†	Day 4†
Baricitinib (Olumiant)§	Daily†	Day 4†
Upadacitinib (Rinvoq)§	Daily†	Day 4†
Not severe SLE: withhold these medications 1 week prior to surgery		
Mycophenolate mofetil	Twice daily	1 week after last dose†
Azathioprine	Daily or twice daily	1 week after last dose
Cyclosporine	Twice daily	1 week after last dose†
Tacrolimus	Twice daily (IV and PO)	1 week after last dose†
Rituximab (Rituxan)	Every 4–6 months	Month 7
Belimumab IV (Benlysta)	Monthly†	Week 5†
Belimumab SC (Benlysta)	Weekly†	Week 2†

* Dosing intervals obtained from prescribing information provided online by pharmaceutical companies. Adapted from the 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons guideline (26). DMARDs = disease-modifying antirheumatic drugs; SLE = systemic lupus erythematosus; IV = intravenous; PO = by mouth; SC = subcutaneous; IL-17 = interleukin-17.
** Correction added on 24 August 2022, after first online publication on 20 June 2022. One of the biologic medications to withhold prior to surgery was omitted from Table 2. Golimumab (Simponi) and the corresponding dosing/timing have been added.
† Recommendation that has changed since 2017.
‡ Severe SLE indicates organ-threatening disease.
§ Drug added for 2022 update.
¶ For patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or all SLE for whom antirheumatic therapy was withheld prior to undergoing total joint arthroplasty, antirheumatic therapy should be restarted once the wound shows evidence of healing, any sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no ongoing nonsurgical site infection, which is typically ~14 days.
# Recommendation pertains to infection risk and does not account for risk of cardiac events or venous thromboembolism.

RESULTS/RECOMMENDATIONS

How to interpret the recommendations

1. All recommendations in this guideline are conditional due to the quality of the evidence (see bolded statements in Table 3). A conditional recommendation means that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients but may not apply to all patients. Because of this, conditional recommendations are preference sensitive and always

Table 3. Recommendations for perioperative management of antirheumatic drug therapy in patients with inflammatory arthritis and those with systemic lupus erythematosus (SLE) undergoing elective total hip arthroplasty (THA) or total knee arthroplasty (TKA)*

Recommendation/strength of recommendation	Level of evidence
For patients with RA, AS, PsA, JIA, or all SLE undergoing THA or TKA, continuing the usual dosing of the following DMARDs through surgery is **conditionally** recommended: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and/or apremilast.†	Low to moderate
For patients with RA, AS, PsA, or JIA undergoing THA or TKA, withholding all biologics, including rituximab, prior to surgery and planning the surgery after the next dose is due is **conditionally** recommended.	Low
For patients with RA, AS, PsA, or JIA undergoing THA or TKA, withholding tofacitinib, baricitinib, and upadacitinib for at least 3 days prior to surgery is **conditionally** recommended.‡	Low
For patients with SLE (not severe) undergoing THA or TKA, withholding the current dose of mycophenolate mofetil, mycophenolic acid, azathioprine, cyclosporine, mizoribine, or tacrolimus 1 week prior to surgery is **conditionally** recommended.	Low
For patients with SLE (not severe) undergoing THA or TKA, withholding the usual dose of belimumab and rituximab prior to surgery is **conditionally** recommended.	Low
For patients with severe SLE who have been deemed appropriate to undergo THA or TKA, continuing the usual dose of mycophenolate mofetil, mycophenolic acid (Myfortic), azathioprine, mizoribine, cyclosporine, or tacrolimus, anifrolumab, and voclosporin through surgery is **conditionally** recommended.‡	Low
For patients with severe SLE undergoing THA or TKA, continuing belimumab and planning surgery in the last month of the dosing cycle of rituximab is **conditionally** recommended.‡	Low
For patients with RA, AS, PsA, or all SLE for whom antirheumatic therapy was withheld prior to undergoing TJA, antirheumatic therapy should be restarted once the wound shows evidence of healing, any sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no ongoing nonsurgical site infection, which is typically ~14 days, is **conditionally** recommended.	Low
For patients with RA, AS, PsA, or all SLE undergoing THA or TKA who are receiving glucocorticoids for their rheumatic condition, continuing their current daily dose of glucocorticoids rather than administering supraphysiologic doses of glucocorticoids on the day of surgery is **conditionally** recommended.	Low

* RA = rheumatoid arthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis; DMARDs = disease-modifying antirheumatic drugs; TJA = total joint arthroplasty.
† Apremilast is a change from the prior recommendation.
‡ Indicates a change from the prior recommendation.

warrant a shared decision-making approach. No strong recommendations are made in this guideline, although no recommendation achieved <80% of the vote, and 4 of the votes were unanimous.

2. For each recommendation, a summary of the supporting evidence or conditions is provided.

3. Therapies that were approved after the end of the original systematic literature review on March 6, 2016 through August 2021 are included in these updated recommendations. Therapies approved after the end of the updated systematic review (March 6, 2016 to August 26, 2021) are not included in these recommendations.

4. PICO questions were combined in the final recommendations for clarity.

Recommendations

For patients with RA, AS, PsA, JIA, or all SLE undergoing elective THA or TKA, continuing the usual dosing of the following disease-modifying antirheumatic drugs (DMARDs) through surgery is conditionally recommended: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and/or apremilast.

This conditional recommendation now includes apremilast, but it is otherwise unchanged from the 2017 guideline. Four observational studies provided additional indirect evidence to the previous systematic literature review and found no relationship between the included drugs and the risk of postoperative infections, although the number of included cases and events were low (11,27–29). Patients with a history of severe or recurrent infections or prior prosthetic joint infection may elect to withhold these medications before surgery.

For patients with RA, AS, PsA, or JIA undergoing elective THA or TKA, withholding all biologics, including rituximab, prior to surgery and planning the surgery after the next dose is due is conditionally recommended.

This recommendation no longer includes patients with SLE, who are addressed separately (see below for rationale) but has not otherwise changed. Table 2 contains the included medications.

This recommendation is conditional because the evidence is indirect and there is a lack of a comparator group in the included studies (27,30). This recommendation was informed by additional new evidence from 2 studies that used administrative claims data to accurately capture the timing of infliximab or abatacept use before THA or TKA and to evaluate associations between biologics timing and outcomes (30,31). In both studies, there was no difference in postoperative outcomes when comparing short medication interruptions of ~1 dosing interval to longer interruptions. Results were similar in an additional study evaluating infliximab or abatacept timing before other types of surgery (32). These studies also showed no difference in outcomes in patients receiving infliximab or abatacept within 1 dosing interval before

surgery, although patients receiving intravenous abatacept within 2 weeks of surgery (one-half of a dosing interval) had a numerically higher rate of adverse events that was not statistically significant (31).

Planning the surgery after the end of the dose interval was favored because active drug levels would be low. For example, for rituximab, dosed every 6 months, surgery should be planned during month 7, and for adalimumab, dosed every 2 weeks, surgery should be planned for week 3 (see Table 2 for drug dosing intervals). Patients and their physicians might elect surgery within the dosing cycle if their symptoms from the operative joint are severe and the anticipated pain relief provided by surgery outweighs the possible risk of infection as may occur with advanced osteonecrosis. In addition, those patients whose disease has been challenging to control may also elect to continue their medications rather than risk loss of disease control, as this may occur when medications are withheld.

For patients with RA, AS, PsA, or JIA undergoing THA or TKA, withholding tofacitinib, baricitinib, and upadacitinib for at least 3 days prior to surgery is conditionally recommended.

This conditional recommendation was changed from the prior guideline. For the previous guideline, while the short serum half-life of tofacitinib was known, concern for a longer duration of the immune effect prompted the recommendation to withhold tofacitinib for 7 days prior to surgery. The new recommendation was informed by trial data demonstrating rapid increases in disease activity after interrupting tofacitinib therapy, suggesting a rapid reversal of the immunosuppressive effects, so the recommendation was changed to withhold tofacitinib for 3 days prior to surgery (33). The serum half-life of the newer JAK inhibitors is similar to that of tofacitinib. However, patients and their physicians might withhold JAK inhibitors for a longer period if a patient has a history of infections or a prior prosthetic joint infection. This recommendation does not pertain to the risk of a cardiac event or a venous thromboembolic event (VTE) potentially associated with JAK inhibitors.

For patients with SLE (not severe) undergoing THA or TKA, withholding the current dose of mycophenolate mofetil, mycophenolic acid, azathioprine, cyclosporine, mizoribine, or tacrolimus 1 week prior to surgery is conditionally recommended.

This recommendation remains unchanged from the prior guideline. Patients with frequent flares or SLE that is difficult to control might continue their medications, but the majority could be followed up closely after surgery to address a flare.

For patients with SLE (not severe) undergoing THA or TKA, withholding the usual dose of belimumab and rituximab prior to surgery is conditionally recommended.

This recommendation is unchanged from the prior guideline. Patients with SLE that is not severe would not be at risk for permanent organ damage should they flare. In addition, nonsevere SLE patients could be followed up closely after surgery, and an intervention could be made to treat a flare as needed. Patients with frequent flares or SLE that is difficult to control might choose to continue their medications in a shared decision-making approach with their physicians, but the majority could be followed up closely after surgery to address a flare.

For patients with severe SLE (Table 1) who have been deemed appropriate to undergo THA or TKA, continuing the usual dose of mycophenolate mofetil, mycophenolic acid (Myfortic), azathioprine, mizoribine, cyclosporine, or tacrolimus, anifrolumab, and voclosporin through surgery is conditionally recommended.

This recommendation has changed with the addition of anifrolumab and voclosporin, recently introduced medications for severe SLE. These medications should be continued through surgery. There were no new data available to update this recommendation, so the guidance reflects the concern about disease flares and the risk of organ damage in severe SLE that could be precipitated by medication withdrawal; although postoperative adverse events are linked to disease severity, they have not been clearly associated with medication use. As noted in the previous guideline, the patient's rheumatologist should be consulted regarding medication management. A patient with severe SLE who has been stable for >6 months or who has a history of recurrent or severe infections might discontinue the medications in the perioperative period.

For patients with severe SLE undergoing THA or TKA, continuing belimumab and planning surgery in the last month of the dosing cycle of rituximab is conditionally recommended.

In the prior guideline, rituximab was included in the recommendations with other biologics, but increased use for SLE treatment, the long dosing interval for rituximab, and the indication of belimumab as therapy for severe SLE manifestations has informed this change. Surgery should be planned at the end of the dosing cycle, typically during month 5 or 6 for patients receiving rituximab every 6 months, and to avoid disruptions of therapy rather than wait longer, given the long dosing interval for rituximab. The panel noted that rituximab is used in SLE without an indication approved by the US Food and Drug Administration (FDA) but also noted that it has been included in SLE treatment guidelines (34). In addition, there is a risk of disease flares in patients with severe SLE with organ damage if therapy is interrupted. Situations such as prior severe infections and/or SLE that has been stable for >6 months might prompt the clinician to withhold rituximab for a longer period. Recent studies describe an increased risk of adverse events associated with SLE that appears to be more significant for THA than TKA, but there are no strong data to suggest that these outcomes are related to medication management (34–37).

This recommendation has changed since the prior guideline in part because of the additional indication for the use of belimumab in severe SLE including nephritis, as well as increased

comfort with belimumab among clinicians and patients given its widespread use, low infection risk described in clinical trials, and inclusion in SLE treatment guidelines (34,38,39). The panel remained concerned about disruptions of successful treatment regimens in patients with severe SLE given the potential for severe organ damage, although belimumab might be withheld in stable patients with a history of prior infections.

For patients with RA, AS, PsA, or all SLE for whom antirheumatic therapy was withheld prior to undergoing total joint arthroplasty, antirheumatic therapy should be restarted once the wound shows evidence of healing, any sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no ongoing nonsurgical site infection, which is typically ~14 days after surgery, is conditionally recommended.

Drugs should be restarted based on the clinical status of the patient and the status of the healing wound. Although there was additional evidence to support this recommendation from the literature review, it was indirect and of very low quality across the critical outcomes. Patients with nonrheumatic diseases were included, or the study did not include a comparator group. In one study using a large Medicare data set, outcomes were better in patients who restarted infliximab within 4 weeks after surgery compared to those who restarted later, but the authors noted that this was likely because postoperative complications led to delays in restarting therapy (30).

Patients and their physicians might elect longer periods of not taking medication given a history of prior severe infections or a history of a prior prosthetic joint infection.

For patients with RA, AS, PsA, or all SLE undergoing THA or TKA who are receiving GCs for their rheumatic condition, continuing their current daily dose of GCs rather than administering supraphysiologic doses of GCs on the day of surgery is conditionally recommended.

This recommendation is unchanged from the previous guideline, with 2 new studies considered. One study found no significant association of supraphysiologic ("stress dose") GC doses with adverse events in SLE patients undergoing THA or TKA, but the sizes of the patient groups were small (35). Another study of 432 patients with RA who underwent THA and TKA concluded that patients with higher GC exposure were more likely to have hyperglycemia and other complications and that the risk of short-term complications is increased by 8.4% for every 10-mg increase in GC dose, and a lower cumulative GC dose was not associated with hypotension (40). Exceptions to this recommendation are unchanged. However, wound healing may be affected by use of low-dose (<5 mg/day) GCs when the cumulative dose is high, which may also contribute to perioperative infection risk. This recommendation does not refer to patients with JIA who may have received GCs during childhood developmental stages or to patients receiving GCs to treat primary adrenal insufficiency or primary hypothalamic disease, all of whom may require supraphysiologic doses of GCs to maintain hemodynamic stability.

DISCUSSION

We have updated the 2017 ACR/AAHKS guideline for the perioperative management of DMARDs, biologics, and GCs for adult patients with RA, SpA including AS and PsA, JIA, and SLE undergoing elective THA or TKA. This guideline is intended for use by clinicians and patients and balances the risk of flares of disease when medications are withheld versus infection risk attributed to the medications when they are continued. This update adds new medications introduced and reviews the studies published since the 2017 ACR/AAHKS guideline that have informed our recommendations. The scope of the guideline has not changed and addresses when to withhold and when to restart disease-modifying therapies, as well as perioperative GC management. Although we included patients in our Voting Panel, we did not reinstate the Patient Panel due to the risk associated with the COVID-19 pandemic, and because we thought it was unlikely that patients' priorities regarding the risk of flare versus the risk of infection would have changed. The updated medication list includes medications introduced to treat RA and SpA, including AS and PsA. We have included perioperative management recommendations for the recently introduced JAK-targeted therapies, baricitinib and upadacitinib, in addition to tofacitinib. We have included new management recommendations for the interleukin-17 (IL-17) blocking agent ixekizumab, the IL-23–blocking drug, guselkumab, and the novel synthetic DMARD apremilast. Anifrolumab, approved by the FDA on July 30, 2021, and voclosporin, approved January 22, 2021, were included in this guideline, although there is no information regarding their use in the perioperative period. They increase the risk of infection, and therefore the use of these medications in patients with severe SLE would merit review by the treating rheumatologist in consideration of surgery. The Voting Panel agreed with their inclusion via email voting.

This guideline is informed by cohort studies including pharmacoepidemiologic studies using large administrative databases. To our knowledge, there have been no randomized controlled trials since the publication of the prior ACR/AAHKS guideline in 2017, so much of the data supporting these recommendations remains largely indirect or of low quality. Similar to the last guideline, the major limitation remains the paucity of high-quality direct evidence regarding the added risk of infection from medication use at the time of THA or TKA; therefore, these recommendations continue to rely on indirect studies describing results in patients without rheumatic diseases or on assumptions or conclusions extrapolated from nonsurgical studies. An additional limitation of this guideline is the lack of participation from other orthopedic surgical specialties such as spine or foot and ankle. Moreover, our literature review focused only on THA and TKA, so concerns

of other surgical specialists may have not been addressed by our focused assessment of THA and TKA. Therefore, we are unable to generalize our recommendations to rheumatic disease patients undergoing other orthopedic surgical procedures, as well as non-orthopedic surgery. However, the principles underlying our recommendations may provide a framework to apply in other surgical settings.

A strength of this guideline is the robust collaboration between orthopedic hip and knee surgeons and rheumatologists, as well as the inclusion of patients, epidemiologists, and specialists in infectious diseases who represent other stakeholders for this project. This multidisciplinary collaboration facilitated the uptake and dissemination of the prior guideline, and it is anticipated that these recommendations will be similarly distributed and used to guide busy clinicians and their patients at the time of THA and TKA. GRADE methodology supports consensus-based recommendations that can be reached based on low-quality evidence across the critical outcomes and transparently rates the strength of the recommendation as well as the quality of the evidence supporting the recommendation (24,41). Because most of the evidence informing this guideline is indirect and/or of low quality, all of the recommendations are conditional. Nonetheless, consensus of the Voting Panel was high. Four recommendations received 100% agreement, and none achieved <80% agreement.

This guideline does not address perioperative prophylaxis or treatment of VTEs or perioperative cardiac assessment, as these are addressed in several other focused publications. JAK inhibitors as a class carry an increased risk of VTE, which is a black box warning from the FDA, which more recently issued a warning regarding increased cardiovascular risk (42). Future research should address an assessment of the perioperative cardiac and VTE risks associated with JAK inhibitors and other factors such as disease activity for which there is no direct evidence.

Perioperative management of rituximab has been a challenge given the long dosing interval of 6 months and the recognized risk of severe infection linked to its use (43–46). In this updated guideline, we have separated the perioperative use of rituximab in SLE from the perioperative management of rituximab in other diseases (46). Although rituximab has an FDA indication for RA, but not for SLE, the 2019 European Alliance of Associations for Rheumatology recommendations for the management of SLE include use of rituximab, providing an additional rationale for our change to separate the recommendations for RA and other rheumatic conditions from those for severe SLE (34). Our recommendations are linked to drug dosing intervals given our assumption that the dosing interval reflects the period of immunosuppression; however, infection risk in patients treated with rituximab may be unrelated to the rituximab dosing interval and is increased in those with hypogammaglobulinemia (47,48). Additional research is needed to increase understanding of the factors contributing to infection risk with rituximab therapy, such as duration of therapy or immunoglobulin levels at the time of surgery.

As previously, the recommendations that form this guideline are not treatment mandates. These recommendations will provide the backbone for a shared decision-making process between patient and physician regarding perioperative medication management around the time of surgery. The previous Patient Panel provided critical insight into the priorities of patients around the time of THA and TKA and the importance of open discussion and consultation between the perioperative physician, the orthopedic surgeon, and the rheumatologist. One patient representative on the current Voting Panel noted the anxiety that patients experience around changes to their medication regimens and urged clinicians to be cognizant of this important issue. Although not all scenarios can be addressed in the scope of a document such as this guideline, the most common scenarios are included, and these recommendations should supplement the usual perioperative clinical assessment, risk benefit discussions, and management for clinical optimization prior to surgery.

We continue to support ongoing research to better inform perioperative management of medications used commonly in rheumatic diseases. While we have added to our information base regarding GC management and the timing of biologic infusion therapy, we still lack high-level data from randomized controlled trials to provide clearer answers to the important questions addressed in the guideline. Data concerning traditional synthetic DMARDs should be updated with randomized controlled trials, and data regarding perioperative management of biologics also needs more definitive study. Patients with rheumatic diseases have higher rates of concomitant metabolic syndrome and cardiac disease and may also be at potentially higher risk of perioperative cardiac and/or thromboembolic events. Therefore, consideration of the role of comorbidities and the interaction with antirheumatic therapy should also be pursued.

In summary, this guideline provides an update to the ACR/AAHKS 2017 guideline to provide clinicians and patients information about risks and benefits regarding management of perioperative antirheumatic medication to inform decisions prior to THA and TKA. We have updated our evidence base through our search of the current literature and assessed that information through the lens of our clinical expertise and the perspectives of the patients who have participated in this process. We acknowledge the gaps in our information base and intend to continue to fill those gaps as more research is available.

ACKNOWLEDGMENTS

We thank the ACR staff, including Regina Parker for assistance in coordinating the administrative aspects of the project and Cindy Force for assistance with manuscript preparation. We thank Janet Waters for her assistance in developing the literature search strategy as well as performing the initial literature search and update searches.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Goodman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Goodman, Springer, Klatt, Russell, Sah, Abdel, Johnson, Turner, Yates, Singh.

Acquisition of data. Goodman, Springer, George, Klatt, MacKenzie, Sah, Abdel, Johnson, Mandl, Sculco, Turgunbaev, Yates, Singh.

Analysis and interpretation of data. Goodman, Springer, Chen, Davis, Fernandez, Figgie, Finlayson, George, Giles, Gilliland, Klatt, MacKenzie, Michaud, Miller, Russell, Sah, Abdel, Johnson, Turgunbaev, Yates, Singh.

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Arthritis Care & Research
Vol. 69, No. 8, August 2017, pp 1111–1124
DOI 10.1002/acr.23274
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SPECIAL ARTICLE

2017 American College of Rheumatology/ American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty

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This article is published simultaneously in *Arthritis & Rheumatology* and the *Journal of Arthroplasty*.

Supported by the American College of Rheumatology and the American Association of Hip and Knee Surgeons.

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Objective. **This collaboration between the American College of Rheumatology and the American Association of Hip and Knee Surgeons developed an evidence-based guideline for the perioperative management of antirheumatic drug therapy for adults with rheumatoid arthritis (RA), spondyloarthritis (SpA) including ankylosing spondylitis and psoriatic arthritis, juvenile idiopathic arthritis (JIA), or systemic lupus erythematosus (SLE) undergoing elective total hip (THA) or total knee arthroplasty (TKA).**

Methods. **A panel of rheumatologists, orthopedic surgeons specializing in hip and knee arthroplasty, and methodologists was convened to construct the key clinical questions to be answered in the guideline. A multi-step systematic literature review was then conducted, from which evidence was synthesized for continuing versus withholding antirheumatic drug therapy and for optimal glucocorticoid management in the perioperative period. A Patient Panel was convened to determine patient values and preferences, and the Grading of Recommendations Assessment, Development and Evaluation methodology was used to rate the quality of evidence and the strength of recommendations, using a group consensus process through a convened Voting Panel of rheumatologists and orthopedic surgeons. The strength of the recommendation reflects the degree of certainty that benefits outweigh harms of the intervention, or vice versa, considering the quality of available evidence and the variability in patient values and preferences.**

Results. **The guideline addresses the perioperative use of antirheumatic drug therapy including traditional disease-modifying antirheumatic drugs, biologic agents, tofacitinib, and glucocorticoids in adults with RA, SpA, JIA, or SLE who are undergoing elective THA or TKA. It provides recommendations regarding when to continue, when to withhold, and when to restart these medications, and the optimal perioperative dosing of glucocorticoids. The guideline includes 7 recommendations, all of which are conditional and based on low- or moderate-quality evidence.**

Conclusion. **This guideline should help decision-making by clinicians and patients regarding perioperative antirheumatic medication management at the time of elective THA or TKA. These conditional recommendations reflect the paucity of high-quality direct randomized controlled trial data.**

INTRODUCTION

Although the wide utilization of disease-modifying antirheumatic drugs (DMARDs) and biologic agents has improved the quality of life for patients with rheumatoid arthritis (RA), spondyloarthritis (SpA), juvenile idiopathic arthritis (JIA), or systemic lupus erythematosus (SLE), rates of total hip arthroplasty (THA) and total knee arthroplasty (TKA) remain high (1–6). Patients with rheumatic conditions report significant improvement in pain and function after THA or TKA, yet critical outcomes such as infection, dislocation, and readmission are reported to be higher for patients with RA, SpA, or SLE (7–10) compared to patients with osteoarthritis. At the time of arthroplasty in a high-volume orthopedic hospital, 46% of RA patients were receiving biologic agents, 67% were receiving nonbiologic DMARDs, and 25% were receiving glucocorticosteroids, while 75% of patients with SLE were receiving immunosuppressive medications, and 15% were receiving glucocorticosteroids. The optimal strategy to manage these medications is not known (11–14). Inherent risk factors for infection, such as overall disability and disease activity/severity, may not be modifiable, but the optimal perioperative management of immunosuppressant therapy around the time of arthroplasty may present an opportunity to mitigate risk (15–19).

In this setting, clinicians require guidance regarding perioperative management of antirheumatic drug therapy. Direct evidence, however, which addresses perioperative management is sparse (20,21). To our knowledge, there are no randomized controlled trials (RCTs) evaluating the cessation and reintroduction of biologic agents at the time of THA or TKA. The relevant outcomes considered for these guidelines are the potential increase in infection risk added by the medications versus the risk of disease

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Dr. Springer has received honoraria from Ceramtec (less than $10,000) and consulting fees from Stryker Orthopaedics and Convatec (more than $10,000 each). Dr. Abdel owns stock in Imagen Technologies. Dr. Giles has received consulting fees from Genentech (less than $10,000). Dr. Johnson has received consulting fees from TREG (less than $10,000). Dr. Lee has received consulting fees from EMD Serono (less than $10,000). Dr. Mandl has received consulting fees from UpToDate (less than $10,000). Dr. Sporer has received consulting fees from DJO Surgical Products (more than $10,000), and from OsteoRemedies and PixarBio (less than $10,000 each). Dr. Losina has received honoraria as Deputy Editor of *Journal of Bone and Joint Surgery* (more than $10,000). Dr. MacKenzie has received consulting fees from ArmadaHealth (less than $10,000). Dr. Mikuls has received consulting fees from Pfizer (less than $10,000) and research grants from Astra Zeneca and Bristol-Myers Squibb. Dr. Sah has received speaking fees and/or honoraria from Pacira, Medtronic, Zimmer Surgical Specialties, and Convatec (less than $10,000 each) and from Smith & Nephew and Mallinckrodt (more than $10,000 each). Dr. Singh has received consulting fees from Takeda (more than $10,000) and from Savient, Regeneron, Merz, Iroko, Bioiberica, Crealta/Horizon, Allergan, WebMD, and UBM LLC (less than $10,000 each), research grants from Takeda and Savient and was principal investigator for an investigator-initiated study funded by Horizon through a grant to Dinora (more than $10,000).

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Submitted for publication September 26, 2016; accepted in revised form April 28, 2017.

Significance & Innovations

- Patients with rheumatic diseases undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA) are at increased risk for periprosthetic joint infection.
- Appropriate management of antirheumatic medication in the perioperative period may provide an important opportunity to mitigate risk.
- Nonbiologic disease-modifying antirheumatic drugs may be continued throughout the perioperative period in patients with rheumatic diseases who are undergoing elective THA and TKA.
- Biologic medications should be withheld as close to 1 dosing cycle as scheduling permits prior to elective THA and TKA and restarted after evidence of wound healing, typically 14 days, for all patients with rheumatic diseases.

flare when the medications are withheld. This guideline pertains only to adult patients with RA, SpA including ankylosing spondylitis (AS) and psoriatic arthritis (PsA), JIA, or SLE, who are undergoing elective THA or TKA, and incorporates patient preferences.

This guideline addresses management of antirheumatic medication in those adult patients with diagnoses of RA, SpA, JIA, or SLE, but is not limited to those who meet classification criteria. This guideline is to be used for those who have elected and have been deemed appropriate candidates for THA or TKA. We would caution against extrapolation of this guideline to other orthopedic procedures until further data are available.

This guideline is intended for use by clinicians, including orthopedists, rheumatologists, and other physicians performing perioperative risk assessment and evaluation, as well as patients. The guideline addresses common clinical situations, but may not apply in all exceptional or unusual situations. It is imperative that open and informed communication between the patient, orthopedic surgeon, and rheumatologist takes place. In addition, while cost is a relevant factor in health care decisions, it was not considered in this project.

The populations included in this guideline are shown in Table 1 (22–24). Figure 1 contains a list of the drugs included in the evaluation, along with their dosing intervals, as the Panel determined that the dosing interval and route were more relevant for this guideline because they reflect the duration of effect.

This guideline does not address indications for THA or TKA, medical decisions unrelated to antirheumatic drug therapy, choice of implant, surgical approach, or perioperative evaluation and management of concurrent disease, such as that affecting the cervical spine of patients with RA. Although patients with RA, SpA, JIA, or SLE should be assessed for risk of venous thromboembolism and major acute coronary event (8,25), this guideline does not address cardiac risk assessment or perioperative venous thromboembolism prophylaxis; both are covered in existing guidelines (26–29).

METHODS

Overall methodology. This guideline follows the American College of Rheumatology (ACR) guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of the available evidence and to develop the recommendations (30). Conflicts of interest and disclosures were

Table 1. Populations included in the guideline*

Populations†
Adults age ≥18 years diagnosed with rheumatoid arthritis, spondyloarthritis including ankylosing spondylitis and psoriatic arthritis, juvenile idiopathic arthritis, or SLE (see below), who are deemed to be appropriate surgical candidates, undergoing elective total hip arthroplasty or total knee arthroplasty, and who are treated with antirheumatic drug therapy at the time of surgery.
SLE
SLE includes patients with severe or not severe SLE (defined below), and who are in optimal condition for surgery:
Severe SLE
Currently treated (induction or maintenance) for severe organ manifestations: lupus nephritis, central nervous system lupus, severe hemolytic anemia (hemoglobin <9.9), platelets <50,000/ml, vasculitis (other than mild cutaneous vasculitis), including pulmonary hemorrhage, myocarditis, lupus pneumonitis, severe myositis (with muscle weakness, not just high enzymes), lupus enteritis (vasculitis), lupus pancreatitis, cholecystitis, lupus hepatitis, protein-losing enteropathy, malabsorption, orbital inflammation/myositis, severe keratitis, posterior severe uveitis/retinal vasculitis, severe scleritis, optic neuritis, anterior ischemic optic neuropathy (derived from the SELENA–SLEDAI Flare Index and BILAG 2004) (22–24).
Not severe SLE
Not currently treated for manifestations listed under Severe SLE.

* SLE = systemic lupus erythematosus; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; BILAG = British Isles Lupus Assessment Group.
† All patients carrying the diagnoses listed, without restriction to those meeting classification criteria.

DMARDs: CONTINUE these medications through surgery.	**Dosing Interval**	**Continue/Withhold**
Methotrexate	Weekly	Continue
Sulfasalazine	Once or twice daily	Continue
Hydroxychloroquine	Once or twice daily	Continue
Leflunomide (Arava)	Daily	Continue
Doxycycline	Daily	Continue
BIOLOGIC AGENTS: STOP these medications prior to surgery and schedule surgery at the end of the dosing cycle. RESUME medications at minimum 14 days after surgery in the absence of wound healing problems, surgical site infection, or systemic infection.	**Dosing Interval**	**Schedule Surgery (relative to last biologic agent dose administered) during**
Adalimumab (Humira)	Weekly or every 2 weeks	Week 2 or 3
Etanercept (Enbrel)	Weekly or twice weekly	Week 2
Golimumab (Simponi)	Every 4 weeks (SQ) or every 8 weeks (IV)	Week 5 Week 9
Infliximab (Remicade)	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Abatacept (Orencia)	Monthly (IV) or weekly (SQ)	Week 5 Week 2
Certolizumab (Cimzia)	Every 2 or 4 weeks	Week 3 or 5
Rituximab (Rituxan)	2 doses 2 weeks apart every 4-6 months	Month 7
Tocilizumab (Actemra)	Every week (SQ) or every 4 weeks (IV)	Week 2 Week 5
Anakinra (Kineret)	Daily	Day 2
Secukinumab (Cosentyx)	Every 4 weeks	Week 5
Ustekinumab (Stelara)	Every 12 weeks	Week 13
Belimumab (Benlysta)	Every 4 weeks	Week 5
Tofacitinib (Xeljanz): STOP this medication 7 days prior to surgery.	Daily or twice daily	7 days after last dose
SEVERE SLE-SPECIFIC MEDICATIONS: CONTINUE these medications in the perioperative period.	**Dosing Interval**	**Continue/Withhold**
Mycophenolate mofetil	Twice daily	Continue
Azathioprine	Daily or twice daily	Continue
Cyclosporine	Twice daily	Continue
Tacrolimus	Twice daily (IV and PO)	Continue
NOT-SEVERE SLE: DISCONTINUE these medications 1 week prior to surgery	**Dosing Interval**	**Continue/Withhold**
Mycophenolate mofetil	Twice daily	Withhold
Azathioprine	Daily or twice daily	Withhold
Cyclosporine	Twice daily	Withhold
Tacrolimus	Twice daily (IV and PO)	Withhold

Figure 1. Medications included in the 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. Dosing intervals were obtained from prescribing information provided online by pharmaceutical companies. DMARDs = disease-modifying antirheumatic drugs; SQ = subcutaneous; IV = intravenous; SLE = systemic lupus erythematosus; PO = oral.

managed according to ACR policy (available at www.rheumatology.org/Portals/0/Files/Perioperative-Management-Guidelines-Disclosure-Summary.pdf). The full methods are presented in Supplementary Appendix 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23274/abstract).

Using GRADE, a recommendation can be either in favor of or against the proposed intervention and either strong or conditional (31,32). Much of the evidence was indirect, coming from nonsurgical studies, and all evidence was low to moderate quality (33,34). A strong recommendation indicates that most or almost all informed patients would choose the recommended action. Conditional recommendations are those in which the majority of the informed patients would choose to follow the recommended course of action, but a minority might not (35,36).

Teams involved. This project was a collaboration between the ACR and the American Association of Hip and Knee Surgeons (AAHKS). All participating teams contained representatives from both organizations, including a Core Leadership Team for project oversight (5 members), the Literature Review Team, who reviewed the literature and compiled the literature report, the Expert Panel, who helped frame the scope of the project, and the Voting Panel (consisting of orthopedic surgeons, rheumatologists, an infectious disease expert, an SLE expert, patient representatives, rheumatology methodologists, and a GRADE expert), who determined the final recommendations (for a complete listing of Panel and Team members see Supplementary Appendix 2 [available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23274/abstract]). Additionally, a Patient Panel consisting of 11 adults with RA or JIA, all of whom had undergone THA or TKA, reviewed the evidence and provided input on their values and preferences.

PICO (population/intervention/comparator/outcomes) question development and importance of outcomes. The Core Leadership Team initially drafted the project scope, key principles, and relevant clinical PICO questions, which were then presented to the Expert Panel, the Voting Panel, and the Literature Review Team for their review at a face-to-face meeting where the project plan was defined. The relevant topics addressed included: 1) Should antirheumatic medications be withheld prior to elective THA/TKA? 2) If they are withheld, when should they be stopped? 3) If withheld, when should they be restarted after surgery? 4) In patients receiving glucocorticoids, what dose should be administered at the time of surgery? The full list of PICO questions is shown in Supplementary Appendix 3 (http://onlinelibrary.wiley.com/doi/10.1002/acr.23274/abstract).

Direct high-quality RCT data available comparing the risk of THA or TKA in those receiving versus not receiving the medications of interest, or comparing the background risk of THA and TKA in the populations of interest, were sparse. To address this gap, 2 questions were included to inform the recommendations. The first asked, "What is the background risk for serious adverse events including infections, or hospitalization, associated with use of each of the candidate drugs in patients not undergoing surgery?" The second question asked, "What is the background risk of adverse events associated with THA or TKA, independent of use of candidate medications in the populations of interest?" The group determined that both superficial and deep surgical site infection (reported within the first year after surgery), non–surgical site infection (within 90 days of surgery), and disease flare were the most critical outcomes; other outcomes such as hospital readmission, death, and long-term arthroplasty outcome were also deemed relevant.

Systematic synthesis of the literature and evidence processing. Systematic literature searches were performed in Embase (searched since 1974), the Cochrane Library, and PubMed (searched since the mid-1960s) from January 1, 1980 through March 6, 2016. The search strategies were developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for PubMed and Cochrane Library and Emtree terms for Embase (see Supplementary Appendix 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23274/abstract). Text words were used in PubMed and Embase, and keyword/title/abstract words in the Cochrane Library. Searches resulted in 2,230 total references (see Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/acr.23274/abstract). A final search update was performed for the time period of January 1 to September 8, 2016, using the inclusive search terms of the disease states, coupled separately with "arthroplasty"; no randomized trials were identified that were relevant to the guideline. DistillerSR software (http://systematic-review.net/) was used to screen the literature search results grouped by their match with the pertinent PICO questions.

The Literature Review Team analyzed and synthesized data from eligible studies. Due to the lack of RCTs, we were unable to prepare GRADE Summary of Findings tables for most PICO questions. Microsoft Excel was used for abstracting data from observational studies. When available, the evidence summaries included the benefits and harms for outcomes of interest across studies, the relative effect (with 95% confidence interval [95% CI]), the number of participants, and the absolute effects. We rated the quality of evidence for each critical and important outcome as high, moderate, low, or very low quality, taking into account limitations of study design (including the risk of bias), inconsistency, indirectness, imprecision, and other considerations (including publication bias).

Moving from evidence to recommendations. The Patient Panel attached far greater importance to infection at the time of surgery than to flares. They were unable to precisely quantify the difference in value, noting that it was greater than 10:1.

The Voting Panel met to decide the final recommendations. The Panel discussed the evidence in the context of both their clinical experience and the input from the Patient Panel. The Panel voted anonymously, and 80% agreement defined the threshold for a recommendation; if 80% agreement was not achieved during an initial vote,

the Panel members held additional discussions before revoting. Considerations that led to rating down of quality of evidence included indirectness (much of the evidence came from RCTs outside of the surgical context, or from foot or spine procedures in which infection risks may vary markedly from THA or TKA); heterogeneity in baseline medication dose and duration, particularly relevant in studies addressing glucocorticoid "stress-dose" therapy; and imprecision associated with small sample size.

All recommendations were supported by more than 80% of the Panel, and all but 1 were supported unanimously. In some instances, the Panel combined PICO questions into 1 final recommendation. For recommendations to withhold a medication, a recommendation for the suggested timing of surgery in relation to the last drug-dose was included.

RESULTS/RECOMMENDATIONS

How to interpret the recommendations

1. All recommendations in this guideline are conditional due to the quality of the evidence (see bolded statements in Table 2). A conditional recommendation means that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but may not apply to all patients. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. No strong recommendations are made in this guideline.
2. For each recommendation, a summary of the supporting evidence or conditions is provided.
3. Therapies that were approved after the original systematic literature review are not included in these recommendations.
4. PICO questions were combined in the final recommendations for clarity.

Recommendations

1. RA, SpA including AS and PsA, JIA, and SLE receiving nonbiologic DMARDs

Continue the current dose of methotrexate, leflunomide, hydroxychloroquine, and/or sulfasalazine for patients undergoing elective THA or TKA (Table 2).

This conditional recommendation was based on low- to moderate-quality evidence. A systematic review of literature, which included RCTs of continuing versus discontinuing DMARDs at the time of surgery, revealed that the risk of infections was in fact decreased, with continuing DMARDs having a relative risk (RR) of 0.39 (95% CI 0.17–0.91) (37,38). The evidence base is rated down from high to moderate for reduction in infection risk after orthopedic surgery when these drugs are continued, because of risk of bias. There is indirect evidence describing a low infection risk with these specific DMARDs in settings other than THA and TKA (39). This recommendation was based on infection risk, although flares are also less frequent after surgery in those who continue DMARDs, and the RRs of flares when DMARDs are continued versus stopped (RR 0.06 [95% CI 0.0–1.10]) were derived from low-quality evidence (37,40).

2. RA, SpA including AS and PsA, JIA, or SLE

Withhold all current biologic agents prior to surgery in patients undergoing elective THA or TKA, and plan the surgery at the end of the dosing cycle for that specific medication (Table 2).

This recommendation was based on evidence that was rated down in quality for indirectness, as no RCTs were performed in patients undergoing THA or TKA. We abstracted data from a systematic review of literature that included systematic reviews and meta-analyses of biologic agents versus placebo (and occasionally versus control treatment including nonbiologic DMARDs) in nonsurgical patients, which revealed that the risk of serious infections was increased with biologic agents, with most odds/hazards/risk ratios ~1.5 (range 0.61–8.87) and a higher risk of serious adverse events with most odds/hazards/risk ratios ~1.5 (range 0.33–2.54) (41–87). Our systematic review did not provide ample evidence that would support a differential risk of serious infection among available biologic agents (41–87). Because avoiding infection was significantly more important to patients than flares in the postoperative period, the Panel did not support separating biologic agents regarding infection risk in the perioperative period until further studies clarify and establish differences in risk (41–87). The literature review also revealed that the risk of postoperative infection complications after total joint arthroplasty (TJA) was increased in patients with RA nearly 2-fold, and deep infection complications increased by 1.5-fold (2,56); in SLE, overall postoperative complications were increased 1.3-fold, and septicemia by 2-fold (8), although medication use at the time of surgery was not always reported. In addition, a systematic review, meta-analysis, and network meta-analysis revealed that infection risk for biologic agents is strongly associated with high-dose therapy (higher dose than the standard) and may not be associated with low-dose biologic agents (42), so serum half-life may not correspond to the duration of the immunosuppressant effect. The dosing cycle was therefore chosen as more relevant in determining the withholding interval (88–91) and timing the surgery at the end of the dosing interval at the nadir of the drug effect.

With regard to patients with SLE, a systematic review of literature that included systematic reviews and meta-analyses of rituximab versus placebo (and occasionally versus control treatment including nonbiologic DMARDs) in nonsurgical patients with RA and SLE revealed the risk of serious infections with rituximab with a range of RRs from 0.66 to 0.73 (41,45), and a risk for all serious adverse events with a range of RRs from 0.85 (95% CI 0.62–1.17) to 0.89 (95% CI 0.7–1.14) (59,92). However, most data were indirect and the Panel considered these medications to be similar to tumor necrosis factor inhibitors used for the treatment of RA, which usually have a risk of infection. Moreover, rituximab is not approved by the US Food and Drug Administration (FDA) for treatment of SLE, and belimumab, although FDA-approved for use in SLE, has not been studied in manifestations of severe SLE (e.g.,

lupus nephritis), so the Panel recommended withholding these medications prior to surgery and planning the surgery for the end of the dosing cycle, due to the risk of infection and the paucity of data supporting perioperative benefit in SLE (93–95).

Observational studies reveal that patients with severe or active SLE have a higher risk of adverse events after surgery, but there is no approved role for these biologic agents for patients with severe SLE, including perioperative risk mitigation. SLE manifestations of rash and synovitis are the common clinical indications for belimumab (95,96), and are not thought to increase perioperative risk. There is no direct evidence, however, linking perioperative infection risk to the use of these biologic agents, and little is known about the association of surgical risk with biologic agents for patients with SLE. Since the duration of the immunologic effects of these drugs does not correspond to the serum level, the Panel based the recommendation on the dosing interval (88–91). The Patient Panel did not include patients with SLE, and they were reluctant to vote on SLE medication management strategies because they were uncertain about the value SLE patients would place on flares, which might be organ-threatening, compared to infection risk.

As an example, using this guideline, patients treated with adalimumab, routinely dosed at 2-week intervals, would plan their surgery in week 3, while patients treated with infliximab, when dosed every 8 weeks, would schedule their surgery in the week after the first withheld dose during week 9. Patients treated with rituximab every 6 months would schedule their surgery, when possible, at the week after the first withheld dose during month 7. Patients with SLE receiving belimumab, which is given every 4 weeks, would schedule their surgery during week 5.

3. RA, SpA including AS and PsA, or JIA

Withhold tofacitinib for at least 7 days prior to surgery in patients with RA, SpA including AS and PsA, or JIA undergoing THA or TKA (Table 2).

This recommendation was based on indirect evidence from systematic reviews and meta-analyses of tofacitinib versus placebo (and occasionally versus control treatment including nonbiologic DMARDs) in nonsurgical patients showing that the risk of serious infections was increased with tofacitinib, with an incidence rate of 2.91 (95% CI 2.27–3.74) (97) and higher risk of all infections, with an RR of 5.7 (95% CI 1.8–18.1) (48). Although this drug has an extremely short serum half-life, little is known about the duration of immunosuppression after the drug is withheld, although indirect translational data suggest that host defense returns to normal at 7 days. Therefore, the Panel recognized that the recommendation for the duration of withholding may change in the future, as physician and patient experience with this drug grows (41,47,48,51,77,79,97,98).

4. Severe SLE (as defined in Table 1)

Continue the current dose of methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus through the surgical period in all patients undergoing THA or TKA (Table 2).

There is a great deal of uncertainty and little published experience regarding risks associated with perioperative medication management in patients with severe SLE. There is, however, indirect evidence concerning organ transplant patients who continue anti-rejection therapy through the surgical period (99,100). The caveat to this analogy is that the time course of organ rejection after withholding immunosuppressant medication may be different from the time to SLE flare after withholding medications. These considerations led to the recommendation to continue the current dose of methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus through the surgical period in all patients with severe SLE. Nevertheless, the Panel felt that decisions regarding elective surgery in patients with severe SLE should be made on an individual basis with the patient's rheumatologist.

5. Not-severe SLE (as defined in Table 1)

Withhold the current dose of mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus 1 week prior to surgery in all patients undergoing THA or TKA (Table 2).

For patients with not-severe SLE, the time course to flares after withholding medications is not known, while there is a known infection risk associated with these medications. The Panel felt that careful monitoring of the patient after surgery would permit restarting the medications prior to clinical flares in patients with not-severe SLE, for whom the morbidity of infection might outweigh the risk of a flare. These medications can be withheld 1 week prior to surgery, permitting some return of normal immune function, and restarted at 3–5 days after surgery in the absence of wound healing complications or infection at the surgical site or elsewhere. There are multiple mechanisms postulated for immunosuppression with these medications, including leukopenia, interference with T cell costimulatory signaling, and blocking the de novo pathway of purine synthesis, with different time courses for onset and reversal (101,102).

6. RA, SpA including AS and PsA, JIA, or SLE

Restart biologic therapy in patients for whom biologic therapy was withheld prior to undergoing THA or TKA once the wound shows evidence of healing (typically ~14 days), all sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no clinical evidence of non–surgical site infections (Table 2).

The decision to restart antirheumatic therapy can be based on evaluation of the patient's wound status and clinical judgment for absence of surgical and non–surgical site infections; wound closure is typically reached by 14 days. Therefore, biologic therapy can be restarted once the wound shows evidence of healing (typically ~14 days), all sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no clinical evidence of

Table 2. Recommendations for perioperative management of antirheumatic drug therapy in patients with rheumatic diseases undergoing elective THA or TKA*

Recommendation/strength of recommendation (bold indicates conditional)	Level of evidence
RA, SpA including AS and PsA, JIA, or SLE: Continue the current dose of methotrexate, leflunomide, hydroxychloroquine, and/or sulfasalazine (nonbiologic DMARDs) for patients undergoing elective THA or TKA. • RCTs of continuing vs. discontinuing DMARDs at the time of surgery revealed that the risk of infections was not increased, but in fact decreased, when DMARDs were continued, with an RR of 0.39 (95% CI 0.17–0.91) (37,38). Evidence indicates a low infection risk with these DMARDs in settings other than THA and TKA (39). • Disease flares after surgery occur frequently, and continuing DMARDs decreases the risk (RR 0.06 [95% CI 0.0–1.10]) (37,40), yet flares were significantly less important than infection for the Patient Panel.	Low to moderate
RA, SpA including AS and PsA, JIA, or SLE: Withhold all current biologic agents (see Figure 1) prior to surgery in patients undergoing elective THA or TKA, and plan the surgery at the end of the dosing cycle for that specific medication. • RCTs (nonsurgical) demonstrated an increase in infection risk associated with use of all biologic agents (41–87). • Avoiding infection was significantly more important to patients than flares for patients with RA and JIA. • Meta-analysis and network meta-analysis revealed that infection risk for biologic agents is strongly associated with high-dose therapy and may not be associated with low-dose biologic agents (42). • Serum half-life may not correspond to the duration of the immune-suppressant effect, so the dosing cycle was chosen as more relevant in determining the withholding interval (88–91). • Until further studies have clarified and established differences in risk between biologic agents, there was insufficient evidence to support separating biologic agent management in the perioperative period (43–89). • For SLE, there was paucity of data supporting perioperative benefit in SLE (93–95). • A systematic review of rituximab vs. placebo (and occasionally vs. control treatment including nonbiologic DMARDs) in nonsurgical patients with RA and SLE revealed the risk of all serious adverse events with a range of RRs from 0.85 (95% CI 0.62–1.17) to 0.89 (95% CI 0.7–1.14) (59,92). • Observational studies reveal that patients with SLE, particularly those with active or severe SLE, are at a higher risk for adverse events after surgery. • Belimumab is indicated for use in not-severe SLE, which is not thought to increase perioperative risk (95,96). • As an example, using this guideline, patients treated with rituximab every 6 months would schedule their surgery, when possible, at the week after the first withheld dose during month 7. Patients receiving belimumab, which is given every 4 weeks, would schedule their surgery during week 5. • Patients treated with adalimumab, dosed at 2-week intervals, would plan their surgery in week 3, while patients treated with infliximab, when dosed every 8 weeks, would schedule their surgery in the week after the first withheld dose during week 9.	Low
RA, SpA including AS and PsA, or JIA: Withhold tofacitinib for at least 7 days prior to surgery in patients undergoing THA or TKA. • Indirect evidence from systematic reviews and meta-analyses of tofacitinib vs. placebo (and occasionally vs. control treatment including nonbiologic DMARDs) in nonsurgical patients shows that the risk of serious infections was increased with tofacitinib with an incidence rate of 2.91 (95% CI 2.27–3.74) (97) and higher risk of all infections with an RR of 5.7 (95% CI 1.8–18.1) (48). • Although this drug has an extremely short serum half-life, little is known about the duration of immunosuppression after the drug is withheld. Therefore, the Panel recognized that the recommendation for the duration of withholding may change in the future, as physician and patient experience with this drug grows (41,47,48,51,77,79,97,98).	Low
Severe SLE: Continue the current dose of mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus through the surgical period in all patients undergoing THA or TKA (see Figure 1). • The Panel recognized that there is a great deal of uncertainty and little published experience regarding risks associated with perioperative medication management in patients with severe SLE. • Indirect evidence with organ transplant patients supports continuing anti-rejection therapy without interruption at the time of surgery (99,100). • Decisions regarding elective surgery in patients with severe SLE should be made on an individual basis with the patient's rheumatologist.	Low

(continued)

Table 2. *(Cont'd)*

Recommendation/strength of recommendation (bold indicates conditional)	Level of evidence
SLE (not severe): Withhold the current dose of mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus 1 week prior to surgery in all patients undergoing THA or TKA. • The time course to flares in not-severe SLE is not known. • The morbidity of prosthetic joint infection may be more severe than a flare in SLE that is not severe. • These medications can be withheld 1 week prior to surgery, permitting return of some immune function, and restarted at 3–5 days after surgery in the absence of wound healing complications or infection at the surgical site or elsewhere. • There are multiple mechanisms postulated for immunosuppression with these medications, including leukopenia, interference with T cell costimulatory signaling, and blocking the de novo pathway of purine synthesis, with different time courses for onset and reversal (101,102). • Suggest a conservative withhold of 7 days prior to surgery until additional research increases understanding of these medications.	Low
RA, SpA including AS and PsA, JIA, or SLE: Restart biologic therapy in patients for whom biologic therapy was withheld prior to undergoing THA and TKA once the wound shows evidence of healing (typically ~14 days), all sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no clinical evidence of non–surgical site infections, rather than shorter or longer periods of withholding. • The decision to restart antirheumatic therapy should be based on careful assessment of the patient's wound status and clinical judgment for absence of surgical and non–surgical site infections. Normal wound closure typically requires ~14 days.	Low
RA, SpA including AS and PsA, or SLE: Continue the current daily dose of glucocorticoids in patients who are receiving glucocorticoids for their rheumatic condition and undergoing THA or TKA, rather than administering perioperative supra-physiologic glucocorticoid doses (so-called "stress dosing"). • This recommendation specifically refers to adults with RA, AS, PsA or SLE who are receiving glucocorticoids for their rheumatic condition, and does not refer to JIA patients receiving glucocorticoids who may have received glucocorticoids during childhood developmental stages, or to patients receiving glucocorticoids to treat primary adrenal insufficiency or primary hypothalamic disease. • The literature review found information on hemodynamic instability in a systematic literature review on patients with rheumatic diseases whose mean prednisone (or equivalent) dose was ≤16 mg/day. • The CDC considers the cut-off for immunosuppression at 20 mg of prednisone/day for at least 2 weeks, and observational studies demonstrate an increase in arthroplasty infection risk with long-term steroid use >15 mg/day. • Optimization for THA and TKA should include carefully tapering the glucocorticoid dose prior to surgery to <20 mg/day, when possible (102,103).	Low

* THA = total hip arthroplasty; TKA = total knee arthroplasty; RA = rheumatoid arthritis; SpA = spondyloarthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis; SLE = systemic lupus erythematosus; DMARDs = disease-modifying antirheumatic drugs; RCTs = randomized controlled trials; RR = relative risk; 95% CI = 95% confidence interval; CDC = Centers for Disease Control and Prevention.

non–surgical site infections. There is no direct evidence regarding the optimal time to restart medication after surgery, but standard precautions for biologic agents warn against use in patients with an active infection or in high-risk settings, such as with an open wound.

7. RA, SpA including AS and PsA, or SLE

Continue the current daily dose of glucocorticoids in adult patients with RA, SpA including AS and PsA, or SLE who are receiving glucocorticoids for their rheumatic condition and undergoing THA or TKA, rather than administering perioperative supra-physiologic glucocorticoid doses (so-called "stress dosing") (Table 2).

Hemodynamic instability/hypotension and infection risk were 2 specific areas of concern with regard to perioperative glucocorticoid dosing. Regarding hemodynamic instability, the recommendation to continue the current daily dose of glucocorticoids in adult patients who are receiving glucocorticoids, rather than administering perioperative supra-physiologic glucocorticoid doses ("stress dosing"), specifically refers to adults with RA, AS, PsA, or SLE who are receiving glucocorticoids (≤16 mg/day prednisone or equivalent) for their rheumatic condition; it does not refer to JIA patients receiving glucocorticoids who may have been treated with glucocorticoids during childhood developmental stages, or to patients receiving glucocorticoids to treat primary adrenal insufficiency or primary hypothalamic disease. Low-quality RCT evidence (rated down for indirectness due to varying glucocorticoid doses, heterogeneity of surgical procedures, and imprecision due to small numbers) and evidence from observational trials summarized in a systematic review suggested that there was no significant hemodynamic difference between those patients given their current daily glucocorticoid dose compared to those receiving "stress-dose steroids" (103).

Regarding the infection risk, the Panel noted that the cutoff for immunosuppression according to the Centers for Disease Control and Prevention was 20 mg/day of prednisone for at least 2 weeks, in the context of risk

associated with the administration of live vaccines. In addition, observational studies demonstrate an increase in infection risk following TJA for long-term users of glucocorticoids at doses of >15 mg/day. A patient in optimal condition for elective THA or TKA would be receiving a dose of prednisone or equivalent that was <20 mg/day, when possible, and receive their usual daily dose rather than the "stress dose" in light of the effect on infection risk (102,103).

DISCUSSION

The 2017 ACR/AAHKS guideline for the perioperative management of antirheumatic drug therapy for adults undergoing elective THA and TKA was designed for use by clinicians and patients during the perioperative period. Included recommendations address the use of treatment with antirheumatic drugs (including DMARDs, tofacitinib, biologic agents, and glucocorticoids) for the adult patient with RA, SpA including AS and PsA, JIA, or SLE, recognizing that antirheumatic medication is frequently used at the time of THA or TKA, and that rates of infection and adverse events, including readmission, are increased in this population. The optimal management of antirheumatic medications to treat these diseases may mitigate risks. We have used GRADE methodology to synthesize the best available evidence and have been transparent regarding both the strength of the recommendation and the limited quality of the evidence for each recommendation.

This project brought together major stakeholders (orthopedic arthroplasty surgeons, rheumatologists, methodologists, and patients) to create a patient-centric, expert-led group to determine optimal management of these high-risk patients through a group consensus process. To date, there has been little to no consensus among orthopedic surgeons or rheumatologists on the optimal way to manage antirheumatic medications during the TJA perioperative period, which often leads to uncertainty in decision-making for physicians and patients alike.

A major limitation of this guideline is the paucity of high-quality, direct evidence regarding medications and perioperative risk of infection and flare. The indirect nature of the evidence was the primary reason the quality of evidence was considered low, which led to a conditional designation for all the recommendations. Nonetheless, because patients with rheumatic diseases frequently undergo THA and TKA while receiving DMARDs and biologic agents, we sought to fulfill the need for guidance based on the best available evidence and agreement among stakeholders. The Patient Panel thought infection risk was much more important than flare risk, and this drove the direction of the recommendations (uniformly in favor of withholding any medications in which evidence from nonoperative populations suggested an increase in infection).

Topics such as cardiac risk, deep venous thrombosis risk, risk of 90-day readmissions, and management and care of the cervical spine are related to the perioperative care of patients with rheumatic disease who are undergoing THA or TKA. The guideline was limited, however, to risks attributable to perioperative management of antirheumatic drug therapy.

Antirheumatic medications and disease states were initially evaluated individually. Due to a lack of evidence, however, for each individual medication and disease state, the medications were combined by category and diseases, with the exception of SLE.

With regard to patients with SLE, the Panel recognized that recommendations for perioperative medication management in a complex disease such as SLE would be challenging, as SLE is frequently complicated by multiple organ involvement, as well as complex or unusual medication regimens. Moreover, SLE flares may be organ-threatening, and SLE patients may be more averse to risk of flare than to infection; therefore, the lack of SLE patients on the Patient Panel was a limitation. Nonetheless, the orthopedic and rheumatology stakeholders felt strongly that perioperative medication management guidance was needed for SLE patients.

The recommendation to restart biologic agents was based on the patient's wound healing (generally requiring a minimum of 14 days) and clinical judgment for the absence of both surgical site and non–surgical site infection. While there are differences in practice patterns and many patients do not return to their surgeon within 2 weeks of discharge, screening mechanisms to assess the wound, including utilizing visiting nurse services, and taking photographs of the wound for review by e-mail, smartphone, or other mobile health technologies, would help to identify those who should be evaluated in person prior to restarting biologic agents.

The Voting Panel thought it worthwhile to suggest a research roadmap for future studies that could be conducted as part of a collaboration between the 2 organizations. The team discussed the following topics and recommended that they be targeted for future research: 1) Perioperative glucocorticoid management. While the RCT data support continuing the current glucocorticoid dose rather than "stress dosing," limited numbers of patients and heterogeneity of dose, diagnosis, and surgical procedure leave us with only low-quality evidence; 2) Perioperative management of biologic agents. The Voting Panel suggested investigating existing biologic agents through registries and administrative databases, as well as planning multicenter RCTs to define the optimal medication management strategy; and 3) Perioperative management of DMARDs. Currently, data from RCTs for patients undergoing surgery reflect older, lower-dose regimens for methotrexate, and studies of leflunomide include small numbers of patients. Multicenter RCTs should be performed to determine the optimal perioperative management regimens and include assessment of comorbidities and glucocorticoid use in the study design.

The recommendations that form this guideline are not treatment mandates, but can be used to provide guidance and promote discussion regarding medication management prior to surgery. The authors recognize that not all potential perioperative clinical scenarios are covered by this guideline, but the most common clinical scenarios are addressed. This guideline does not replace perioperative clinical assessment and optimization, and does not

preclude a discussion of the risks and benefits of surgery as patients and their physicians prepare for THA and TKA.

In summary, this guideline provides clinicians and patients with a working document regarding how to manage antirheumatic drugs in the time leading up to elective THA and TKA. The recommendations provide important guidance that was informed by the available literature, clinical expertise and experience, and patient values and preferences. The acknowledgment of low-quality evidence in this area should lay the foundation for future research.

ACKNOWLEDGMENTS

The authors thank Anne Bass, MD, Elie Berbari, MD, Mark Figgie, MD, MBA, Stuart Goodman, MD, PhD, Marc Hochberg, MD, MPH, Eric Matteson, MD, and William Benjamin Nowell, PhD, MSW for serving on the Expert Panel. The authors also thank the Arthritis Foundation and the Global Healthy Living Foundation for their assistance with patient involvement in this guideline project, as well as the patients who participated on the Patient Panel (Katie Acompora, Deserae Constantineau, Marshall Davis, Laureen Fable, Nancy Franklin-Hicks, Jennifer Kangal, Marna McDermott, Tiffany Ann Ohlin, Jodi Pound, Kirsten Smith, and Kelly Voight). We thank the ACR staff, including Ms Regina Parker for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, and Ms Robin Lane for assistance in manuscript preparation. We thank Ms Janet Waters for help in developing the literature search strategy and performing the literature search and updates, and Ms Janet Joyce for reviewing the literature search strategy.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. S. Goodman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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2022 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty

Guideline Summary

Revised July 18, 2022

This updated guideline includes changes in the recommendations regarding rituximab and belimumab for patients with severe SLE, and now includes anifrolumab and voclosporin. For patients with spondyloarthritis, recommendations have been added on management of ixekizumab and guselkumab. The recommendations have changed for management of JAK inhibitors and suggest withholding for 3 days before surgery; tofacitinib, upadicitinib, and baricitinib are now included.

This updated guideline addresses the perioperative management of disease modifying medications for adults with rheumatic diseases, specifically inflammatory arthritis (IA) and systemic lupus erythematosus (SLE) undergoing elective total hip arthroplasty (THA) and total knee arthroplasty (TKA). A panel of rheumatologists, orthopaedic surgeons, and infectious disease specialists updated the systematic literature review and included currently available medications for the clinically relevant population, intervention, comparator, and outcomes (PICO) questions, updating the 2017 recommendations*. As patients with IA and SLE are at increased risk of infection after THA and TKA, these recommendations aim to balance the risk of perioperative infection and the risk of disease flares, recognizing that all flares have an impact on quality of life but a flare in a patient with severe SLE at risk for organ damage warrants unique considerations. This updated guideline includes recently introduced immunosuppressive medications to help decision-making by clinicians and patients regarding perioperative disease modifying medication management for patients with IA and SLE at the time of elective THA or TKA.

MEDICATIONS TO CONTINUE THROUGH SURGERY		
DMARDs: CONTINUE these medications through surgery. (All patients)	**Dosing Interval**	**Recommended timing of surgery since last medication dose**
Methotrexate	Weekly	Anytime
Sulfasalazine	Once or twice daily	Anytime
Hydroxychloroquine	Once or twice daily	Anytime
Leflunomide (Arava)	Daily	Anytime
Doxycycline	Daily	Anytime
Apremilast (Otezla)	***Twice daily***	***Anytime***
SEVERE SLE-SPECIFIC MEDICATIONS††: CONTINUE these medications in the perioperative period in consultation with the treating rheumatologist.	**Dosing Interval**	**Recommended timing of surgery since last medication dose**
Mycophenolate mofetil	Twice daily	Anytime
Azathioprine	Daily or twice daily	Anytime
Cyclosporine	Twice daily	Anytime
Tacrolimus	Twice daily (IV and PO)	Anytime
Rituximab (Rituxan)	***IV Every 4-6 months***	***Month 4-6***
Belimumab (Benlysta)	***Weekly SQ***	***Anytime***
Belimumab (Benlysta)	***Monthly IV***	***Week 4***
Anifrolumab (Saphnelo)†	***IV Every 4 weeks***	***Week 4***
Voclosporin (Lupkynis)†	***Twice daily***	***Continue***

MEDICATIONS TO WITHHOLD PRIOR TO SURGERY***		
BIOLOGICS: WITHHOLD these medications through surgery		**Recommended timing of surgery since last medication dose**
Infliximab (Remicade)	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Adalimumab (Humira)	Every 2 weeks	Week 3
Etanercept (Enbrel)	Every week	Week 2
Golimumab (Simponi)	Every 4 weeks (SQ) or every 8 weeks (IV)	Week 5 Week 9
Abatacept (Orencia)	Monthly (IV) or weekly (SQ)	Week 5 Week 2
Certolizumab (Cimzia)	Every 2 or 4 weeks	Week 3 or 5
Rituximab (Rituxan)	2 doses 2 weeks apart every 4-6 months	Month 7
Tocilizumab (Actemra)	Every week (SQ) or every 4 weeks (IV)	Week 2 Week 5
Anakinra (Kineret)	Daily	Day 2
IL-17-Secukinumab (Cosentyx)	Every 4 weeks	Week 5
Ustekinumab (Stelara)	Every 12 weeks	Week 13
Ixekizumab (Taltz)†	***Every 4 weeks***	***Week 5***
IL-23 Guselkumab (Tremfya)†	***Every 8 weeks***	***Week 9***
JAK inhibitors WITHHOLD this medication 3 days prior to surgery*		
Tofacitinib (Xeljanz):	***Daily or twice daily***	***Day 4***
Baricitinib (Olumiant)†	***Daily***	***Day 4***
Upadacitinib (Rinvoq)†	***Daily***	***Day 4***
NOT-SEVERE SLE: WITHHOLD these medications 1 week prior to surgery	**Dosing Interval**	**1 week after last dose**
Mycophenolate mofetil	Twice daily	**1 week after last dose**
Azathioprine	Daily or twice daily	1 week after last dose
Cyclosporine	Twice daily	**1 week after last dose**
Tacrolimus	Twice daily (IV and PO)	**1 week after last dose**
Rituximab (Rituxan)	Every 4-6 months	Month 7
Belimumab IV (Benlysta)	***Monthly***	***Week 5***
Belimumab SQ (Benlysta)	***Weekly***	***Week 2***

Dosing intervals obtained from prescribing information provided online by pharmaceutical companies.

DMARDs = disease-modifying antirheumatic drugs; SQ = subcutaneous; IV = intravenous; SLE = systemic lupus erythematosus; PO = oral.

*2017 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Anti-rheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty

Shading with Bold italics indicates recommendation that has changed since 2017.

† Drug added for 2022 update.

†† Severe SLE indicates organ threatening disease.

** Recommendation pertains to infection risk and does not account for risk of cardiac events or venous thromboembolism.

***For patients with RA, AS, PsA, or all SLE for whom anti-rheumatic therapy was held prior to undergoing TJA, restarting the anti-rheumatic therapy once the wound shows evidence of healing, any sutures/staples are out, there is no significant swelling, erythema or drainage, and there is no ongoing non-surgical site infection, which is typically about 14 days.

*This summary was approved by the ACR Board of Directors on February 24, 2022. These recommendations are included in a full manuscript, which was published in Arthritis Care and Research and Arthritis & Rheumatology June 19, 2022.**

Revised July 18, 2022

*** How to cite this article:**

Goodman, S.M., Springer, B.D., Chen, A.F., Davis, M., Fernandez, D.R., Figgie, M., et al. American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. Arthritis Care Res 2022. https://doi.org/10.1002/acr.24893

Osteoporosis

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2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Guideline Summary

A panel of adult and pediatric rheumatologists and endocrinologists updated the systematic literature review and included currently available medications for the prevention and treatment of glucocorticoid (GC)-induced osteoporosis. A patient panel was included in this update.

Similar to the 2017 guideline, we recommend risk stratifying patients as being at low, moderate, or high risk of fracture (Adults ≥ 40 years, FRAX® 10-year probability of major osteoporotic fracture < 10 %,10-19%, or ≥ 20% respectively). These cut points were used to stratify PICO questions and weigh potential benefits versus harms, when considering osteoporosis (OP) therapy. For all adults initiating or continuing GC therapy ≥ 2.5mg/day for > 3 months, who have never had fracture risk assessment or been treated with OP therapy, initial clinical fracture risk assessment is strongly recommended over no assessment. Clinical fracture risk factor assessment includes the dose, duration, and pattern of GC use, alcohol use, smoking history, hypogonadism, history of prior fractures, low body weight, significant weight loss, parental history of hip fracture, fall history, thyroid disease, hyperparathyroidism, rheumatoid arthritis, malabsorption, chronic liver disease, inflammatory bowel disease, and height loss. If available, BMD testing is recommended within 6 months of starting GC therapy for adults and every 1-2 years thereafter while continuing GC therapy.

A strong recommendation was made to use oral bisphosphonates (BPs) for adults ≥ 40 years receiving long-term GCs, at high risk for fracture, based on available fracture data in GIOP populations. Other agents including intravenous BPs, PTH/PTHrP, and denosumab (DEN) are also options and are conditionally recommended given lack of fracture prevention data in GIOP populations. The selection between oral and IV BP, PTH/PTHrP, and DEN should be based on patient and physician preferences. Selective estrogen receptor modulators (SERMs) and romosozumab (ROM) may be used in selected patients, after careful consideration of potential harms including thrombosis, stroke, and cardiovascular events.

Table 1: Definitions of selected terms used in the recommendations and upgraded position statements for GIOP

Term	Adults ≥ 40 years of age	Adults < 40 years of age
Major osteoporotic fracture (MOF)	Non-traumatic or pathological fractures of the spine, hip, wrist, or humerus	Non-traumatic or pathological fractures of the spine, hip, wrist, or humerus
Clinical fracture risk assessment	History of GC use, evaluation for falls, fractures, frailty, secondary causes of osteoporosis, FRAX® with GC adjustment, BMD testing	History of GC use, evaluation for falls, fractures, frailty, secondary causes of osteoporosis, BMD testing (FRAX® not validated at age <40 years)

Follow up risk assessment during GC treatment	FRAX® and BMD testing every 1-2 years for untreated patients; BMD testing every 1-2 years for OP-treated patients, whether receiving or completed OP therapy	BMD testing every 1-2 years
FRAX® GC correction	If GC dose is > 7.5 mg/day, multiply the 10-year risk of major osteoporotic fracture by 1.15 and the hip fracture risk by 1.2 *	Not applicable
Fracture risk categories in patients not yet receiving OP treatment		
High	Prior OP fracture (s) **OR** Hip or spine BMD T ≤ -2.5 **OR** FRAX® (GC-Adjusted) 10-year risk of MOF ≥ 20%, hip ≥ 3% **OR** GC ≥ 30mg/day or cumulative GC doses ≥ 5 grams/year	Prior OP fracture (s) **OR** GC ≥ 30mg/day **OR** cumulative GC doses ≥ 5 grams/year
Moderate	FRAX® (GC-Adjusted) 10-year risk of MOF ≥ 10 and < 20%, hip > 1 and < 3%	Continuing GC treatment ≥ 7.5mg/day for ≥ 6 months **AND** (Hip or spine BMD Z score < -3) **OR** (rapid bone loss ≥ 10% at the hip or spine over 1-2 years)
Low	FRAX® (GC-Adjusted) 10-year risk of MOF < 10%, hip ≤ 1%	None of the above risk factors other than GC treatment
Treatments	***Recommended pharmacological treatment strategy***	
Calcium and Vitamin D	In addition to lifestyle modifications, optimized intake of dietary and supplemental calcium and vitamin D based on age-appropriate U.S. Recommended Dietary Allowances.	
Bisphosphonates (BP) Alendronate (oral) Risedronate (oral) Ibandronate (oral/ IV) Zoledronic acid (IV) **PTH & PTHrP Agonists** Teriparatide (TER) Abaloparatide (ABL) **Anti-RANKL** Denosumab (DEN) **SERM** Raloxifene (RAL) Bazedoxifene (BAZ) **Anti-sclerostin** Romosozumab (ROM)	*First line:* *Strong recommendation based on fracture data in GIOP:* Oral BP *Conditional recommendation due to lack of fracture data in GIOP:* IV BP[$], DEN, PTH/PTHrP Conditionally *recommended against due to CVD and thrombosis risk unless first-line therapies are contraindicated or not tolerated: ROM, SERM*	*First line:* *Conditional recommendation* Oral or IV BP[$], PTH/PTHrP or DEN Conditionally *recommended against due to CVD and thrombosis risk unless first-line therapies are contraindicated or not tolerated:* SERM and ROM

BP = bisphosphonate; PTH = parathyroid hormone; PTHrP = PTH-related protein; RANKL = Receptor activator of NF-κβ-Ligand; SERM = Selective estrogen receptor modulator; BMD = bone mineral density; GC= glucocorticoid; FRAX® = https//www.shef.ac.uk/FRAX/Tool.jsp; MOF = major osteoporotic fracture; * FRAX® GC correction example: if hip fracture risk is 2.0% multiply by 1.2 for adjusted risk =2.4%; [$] = IV BP not preferred in women of child-bearing potential

Osteoporosis Medications for Patients with Chronic Kidney Disease or Following Renal Transplant

Bisphosphonates should generally not be used in patients with an eGFR < 35 ml/min. When eGFR is < 35 ml/min, the risk of renal osteodystrophy, including adynamic bone disease, osteomalacia, osteitis fibrosa cystica and mixed uremic osteodystrophy, is increased. As such, metabolic bone disease expert evaluation for chronic kidney disease-mineral and bone disorder (CKD-MBD) is conditionally recommended to exclude these conditions. Once excluded, no dose adjustment is needed when prescribing DEN, PTH/PTHrP, or romosozumab (ROM).

Table 2. Recommendations for initial treatment for prevention of GIOP in adults beginning long-term GC therapy

Recommendations for patients taking prednisone ≥ 2.5mg/day for > 3months	Certainty of evidence	PICO evidence report basis	Page no(s). of evidence tables
For adults and children beginning or continuing chronic GC treatment at low, moderate, or high risk of fracture, optimizing dietary and supplemental calcium and vitamin D in addition to lifestyle modifications (CAL/VIT D/LM) is **conditionally** recommended. All additional recommendations are in addition to CAL/VIT D/LM).	Low or Very Low	1.1a,b,c-1.3a,b,c, 2.1-2.3, 7.16-7.26	6-8, 47-48, 63-65, 141-144,148-151
In adults ≥ 40 years			
With ***LOW*** fracture risk, adding any OP medications to CAL/VIT D /LM based on known harms with no evidence of benefit is **strongly** recommended ***against***.	Very Low	1.4a-1.28a	8-46
With ***MODERATE*** fracture risk, oral or IV BP, PTH/PTHrP, or DEN over no OP therapy is **conditionally** recommended.	Moderate to Very Low	1.4b-1.28b	42-47
With ***MODERATE*** fracture risk, using ROM or SERM is **conditionally** recommended *against* except for in patients intolerant of other agents, due to risk of life-threatening harms.	Very Low	1.12b, 1.16b,1.17b,1.21b-1.25b, 1.28b	40-41, 44-47
With ***HIGH*** fracture risk, oral BP over not giving OP therapy is **strongly** recommended[#]. IV BP, PTH/PTHrP, or DEN over no OP therapy is **conditionally** recommended[$].	Low or Very Low	1.5c-1.28c	48-53
With ***HIGH*** fracture risk, using ROM or SERM is **conditionally** recommended ***against*** except for patients intolerant of other agents due to risk of life- threatening harms	Very Low	1.16c, 1.21c, 1.28c	50, 52-53

With ***HIGH*** fracture risk, using two different OP medications at the same time is **conditionally** recommended ***against***.	Very Low	1.29-1.35	53-62
For *post-menopausal* women at moderate or ***HIGH*** fracture risk, SERM is **conditionally** recommended ***against*** except for in patients intolerant of other agents, due to risk of life- threatening harms.	Very Low	1.12b,c, 1.17b,c 1.22b,c-1.25b,c	43-46, 50-52
Adults ≥ 40 years receiving high-dose GC (initial dose ≥ 30 mg/day or cumulative dose ≥ 5 gm in 1 year)			
Treating with oral or IV BP, PTH/PTHrP, DEN, SERM, or ROM is **conditionally** recommended.	Low	6.4a-6.19a	120-130
In adults <40 years			
With ***LOW*** fracture risk, adding OP medications over CAL/VIT D/ LM alone is **strongly** recommended ***against*** due to known risk of harms and no evidence of benefit.	Very Low	4.4a-4.13a	91-101
With ***MODERATE or HIGH*** fracture risk, oral or IV BP[%], DEN, or PTH/PTHrP therapy is **conditionally** recommended.	Low or Very Low	2.4-2.22, 3.4-3.17	65-76, 79-84.
With ***MODERATE or HIGH*** fracture risk, using ROM is **conditionally** recommended ***against*** due to risk of life-threatening harms.	Very Low	2.9, 3.9	70, 86
Adults < 40 years[#] receiving high-dose GC (initial dose ≥ 30 mg/day > 30 days or cumulative dose ≥ 5 gm in 1 year)			
Treating with oral or IV BP[%], PTH/PTHrP or DEN is **conditionally** recommended over SERM or ROM due to risk of life-threatening harms	Low	6.1b-6.19b	133-141
For adults with solid organ transplants, glomerular filtration rate ≥ 35 ml/minute, and no evidence of chronic kidney disease-mineral and bone disorder (CKD-MBD)*			
Expert evaluation for CKD-MBD in renal transplant recipients is **conditionally** recommended.	Low	5.1-5.26	103-118
Personalized treatment with oral or IV BP, DEN, PTH/PTHrP, or SERM based on individual patient factors is **conditionally** recommended.	Low	5.1-5.26	103-118
Using ROM due to CVD risk and lack of safety in this population is **conditionally** recommended ***against***.	Very Low	5.9	112
Children ages 4-17 years treated with GCs at any dose for > 3 months (Low or moderate risk)			
Optimization of dietary and supplementation of CAL and VIT D is **conditionally** recommended as recommended by U.S. RDA depending on the age of the child.	Very Low	7.1a-7.4a	141-144
Starting oral or IV BP is **conditionally** recommended ***against*** due to low risk of OP fractures in this age group.	Very Low	7.5a	144

Children ages 4-17 years with *an osteoporotic fracture* who are continuing treatment with GCs at a dose of ≥ 0.1 mg/kg/day for > 3 months (high risk)			
Treating with an oral or IV BP is **conditionally** recommended.	Very Low	7.1b-7.2b	147-253

GIOP = Glucocorticoid-induced osteoporosis, BMD = Bone mineral density, GC = glucocorticoids, BP = bisphosphonate, IV = intravenous, DEN = denosumab, PTH/PTHrP = parathyroid hormone/ parathyroid hormone related protein, RAL = raloxifene, ROM = romosozumab, OP = osteoporosis; PICO = Patients, intervention, comparison, outcome; CAL/VIT D/LM = calcium/ vitamin D/ lifestyle modifications; # strong recommendation based on fracture data, $ conditional due to lack of fracture data, % who are not planning on pregnancy during the OP treatment period or are using effective birth control if sexually active; CAL = calcium; CVD = cardiovascular disease; SERM = selective estrogen receptor modulator; U.S. RDA = United States Recommended Dietary Allowances; CKD-MBD = chronic kidney disease-mineral and bone disorder; *includes osteomalacia, adynamic bone disease, osteitis fibrosa cystica, mixed uremic osteodystrophy

This updated guideline includes recommendations on abaloparatide (PTHrP) and romosozumab (ROM), which are newly available since the 2017 guideline. It also addresses sequential therapy, which was not addressed in the past. Patients should know that osteoporosis therapy with denosumab (DEN), teriparatide (PTH), PTHrP, or ROM will need sequential osteoporosis therapy to prevent rapid bone loss after these drugs are discontinued. Recommendations for sequential therapies are based in part on initial study designs, long term follow-up studies, and new clinical trials. Patients completing a course of DEN should transition to 1-2 years of a BP. Patients completing a course of PTH, PTHrP, or ROM need to transition to a BP or DEN. Discontinuation of DEN after two or more doses has been associated with rapid bone loss and development of new vertebral compression fractures as soon as 7-9 months after the last dose. As such, BP therapy is recommended beginning at 6-7 months after the last dose of DEN. The precise timing, dose and duration of BP use after DEN cessation is under study, but treatment for a least 1 year seems prudent, until additional research is available. Stopping PTH/PTHrP without transition to another therapy can also result in rapid bone loss and new fractures, which can be prevented by institution of oral or IV BP or DEN. Stopping ROM without transition to another therapy can result in bone loss, which can be prevented by the institution of oral or IV BP or DEN.

Sequential Treatments Recommended When Initial OP Therapy and GC are Discontinued and at Low or Moderate Risk

Initial OP therapy	**Subsequent OP therapy options**
Oral/IV Bisphosphonate	No subsequent OP therapy needed
SERM	No subsequent OP therapy needed
PTH/PTHrP	Oral or IV Bisphosphonate, **OR** Denosumab followed by Bisphosphonate
Denosumab	Oral or IV Bisphosphonate
Romosozumab	Oral or IV Bisphosphonate, **OR** Denosumab followed by Bisphosphonate

Sequential Treatments Recommended When Initial OP Therapy and GC are Discontinued and Patient Remains High Risk

Continue current therapy or switch to IV Bisphosphonate, DEN, PTH/PTHrP, SERM or romosozumab

This summary was initially approved by the ACR Board of Directors on August 13, 2022 and updated on November 9, 2022. These recommendations are included in a full manuscript, which will be submitted for publication in Arthritis & Rheumatology and Arthritis Care and Research.

ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 8, August 2017, pp 1521–1537
DOI 10.1002/art.40137
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SPECIAL ARTICLE

2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

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This article is published simultaneously in *Arthritis Care & Research*.

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Supported by the American College of Rheumatology.

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Dr. Cannon has received honoraria from Takeda (less than $10,000). Dr. Hansen has received research grants from Takeda and Merck Sharpe & Dohme. Dr. Lane has received consulting fees from Merck (less than $10,000) and has served as an expert witness on behalf of Novartis. Dr. Saha has received consulting fees from UCB Biosciences (more than $10,000). Dr. McAlindon has received consulting fees from Pfizer (less than $10,000).

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Submitted for publication August 26, 2016; accepted in revised form April 20, 2017.

Objective. **To develop recommendations for prevention and treatment of glucocorticoid-induced osteoporosis (GIOP).**

Methods. **We conducted a systematic review to synthesize the evidence for the benefits and harms of GIOP prevention and treatment options. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to rate the quality of evidence. We used a group consensus process to determine the final recommendations and grade their strength. The guideline addresses initial assessment and reassessment in patients beginning or continuing long-term (≥3 months) glucocorticoid (GC) treatment, as well as the relative benefits and harms of lifestyle modification and of calcium, vitamin D, bisphosphonate, raloxifene, teriparatide, and denosumab treatment in the general adult population receiving long-term GC treatment, as well as in special populations of long-term GC users.**

Results. **Because of limited evidence regarding the benefits and harms of interventions in GC users, most recommendations in this guideline are conditional (uncertain balance between benefits and harms). Recommendations include treating only with calcium and vitamin D in adults at low fracture risk, treating with calcium and vitamin D plus an additional osteoporosis medication (oral bisphosphonate preferred) in adults at moderate-to-high fracture risk, continuing calcium plus vitamin D but switching from an oral bisphosphonate to another antifracture medication in adults in whom oral bisphosphonate treatment is not appropriate, and continuing oral bisphosphonate treatment or switching to another antifracture medication in adults who complete a planned oral bisphosphonate regimen but continue to receive GC treatment. Recommendations for special populations, including children, people with organ transplants, women of childbearing potential, and people receiving very high-dose GC treatment, are also made.**

Conclusion. **This guideline provides direction for clinicians and patients making treatment decisions. Clinicians and patients should use a shared decision-making process that accounts for patients' values, preferences, and comorbidities. These recommendations should not be used to limit or deny access to therapies.**

INTRODUCTION

Glucocorticoids (GCs) play an important role in the treatment of many inflammatory conditions. It is estimated that 1% of the US population is treated long-term with GCs (1). However, GC use causes significant toxicity, including bone loss and fractures (2,3). More than 10% of patients who receive long-term GC treatment are diagnosed with a fracture, and 30–40% have radiographic evidence of vertebral fractures (4,5). The highest rate of bone loss occurs within the first 3–6 months of GC treatment, and a slower decline continues with persistent use (6). Both high daily and high cumulative GC doses increase risk of fracture, particularly vertebral fracture, due to the greater effects of GCs on trabecular bone than on cortical bone. Risk factors for GC-induced fracture include low bone strength at the beginning of GC treatment and the rate of decline in bone mass during treatment, which is largely determined by the dose and duration of GC use. In children, GC treatment also affects bone strength, growth, and total adult skeletal mass, with a similar profile of risk factors (7–10).

However, GC treatment is a potentially reversible risk factor for glucocorticoid-induced osteoporosis (GIOP); if GC treatment is terminated, bone mineral density (BMD) increases and fracture risk declines (6,11,12). In addition, the absolute risk of future fracture in an individual is substantially influenced by demographic and other characteristics (age, race, sex, and concomitant OP risk factors). For these reasons, it is important to identify those patients taking GCs for whom the benefits of preventive therapy sufficiently outweigh potential harms.

Numerous risk calculators can be applied in clinical practice to provide estimates of risk of major OP fracture and hip fracture clinically diagnosed, with adjustment for GC dose in some but not all calculators (13–15). Most stratify GC use into 2 categories: low (prednisone ≤7.5 mg/day) or high (>7.5 mg/day), based on data from clinical trials and epidemiologic studies (15,16) demonstrating increasing fracture risk with higher daily doses. However, these calculators may underestimate the fracture risk in patients with prolonged treatment with very high doses of GCs for conditions such as giant cell arteritis, vasculitis, lupus, and dermatomyositis (16,17). Van Staa et al reported a marked increase in relative risk of vertebral and hip fractures in patients who had received treatment with prednisolone ≥30 mg/day with a cumulative dose of >5 gm (15).

There are insufficient data to develop individual prediction tools for children and for adults <40 years of age. Nevertheless, observational data indicate a substantial risk of clinically diagnosed vertebral fracture among premenopausal women ≥30 years of age receiving very high doses of GCs (10-year risk 5–20%) (18–25).

Despite increasing information about risk factors for fracture in GC users and the availability of effective therapies to prevent fracture, many long-term GC users never receive therapy to prevent bone loss or are treated

only after a fracture has occurred (26,27). The American College of Rheumatology (ACR) identified GIOP as an important public health issue and first published recommendations for its prevention and treatment in 1996 (28). The ACR updated these guidelines in 2001 and 2010, as new techniques for assessing fracture risk and new information about risk factors and therapies became available (28–30). The present ACR guideline outlines the treatment recommendations for GIOP. The guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (see below) and included therapies for the treatment of OP approved by the US Food and Drug Administration before 2015. No other therapies have been approved as of the time of publication of these guidelines.

METHODS

Methodology overview. We developed this guideline according to the ACR guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process includes the GRADE methodology (www.gradeworkinggroup.org) (31–33). Conflicts of interest and disclosures were determined and managed according to ACR policy (https://www.rheumatology.org/Portals/0/Files/GIOP-Guidelines-Disclosure-Summary.pdf). The full methods are described in detail in Supplementary Appendix 1 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract). This work involved 4 teams: 1) a Core Leadership Team (4 members), which supervised and coordinated the project and drafted the clinical questions and manuscript; 2) a Literature Review Team, which completed the literature search and abstraction; 3) an Expert Panel, which developed the clinical questions (PICO [population/intervention/comparator/outcomes] questions) and the scope of the guideline project; and 4) a Voting Panel, which included adult and pediatric rheumatologists, internists, a nephrologist, a pulmonologist, a gastroenterologist, medical specialists with clinical expertise in treating GIOP, and a patient who provided input from the patient perspective and voted on the recommendations. Rosters of the team and panel members are shown in Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract).

Framework for the GIOP guideline development. The Panel ranked fracture (hip, vertebral, nonvertebral) as the *critically important outcome measure* for treatment evaluation. *Important outcome measures* included adverse effects of treatments, in particular the incidence of serious and total adverse events (see Supplementary Appendix 3 [http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract] for a list of adverse events).

At the initial meeting, the Voting Panel and Expert Panel agreed that the scope of the project should be the assessment, prevention, and treatment of OP and fractures in children and adults taking glucocorticoids (prednisone at >2.5 mg/day for ≥3 months), including patients with organ transplants, women of childbearing potential, and people receiving very high-dose GCs. Treatment of people using inhaled GCs and those with a glomerular filtration rate of <30 ml/minute were not addressed in these guidelines.

Adult men and women were divided into 2 groups based on age (≥40 years or <40 years). After population risk groups were defined, interventions and comparators for each clinical scenario were specified using a PICO question (see list of PICO questions in Supplementary Appendix 3). PICO questions included assessment and reassessment of fracture risks, treatment comparisons, and questions about duration and reassessment of treatment. When it was necessary to use BMD to support a recommendation (which was the case in only 4 PICO questions, all addressing pediatric patients with GIOP), the Voting Panel downgraded the quality of evidence for indirectness, since BMD provides only indirect evidence of the impact on fracture.

Systematic synthesis of the literature. We performed systematic searches of the published English-language literature including OVID Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from the beginning of each database through October 6, 2015 (Supplementary Appendix 4, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract), and update searches were conducted on April 23, 2016. We performed duplicate screening of literature search results using DistillerSR software (https://distillercer.com/products/distillersr-systematic-review-software/) (Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract). Data were extracted into RevMan software (http://tech.cochrane.org/revman), and the quality of each study was evaluated using the Cochrane risk of bias tool (http://handbook.cochrane.org/). We exported RevMan files into GRADEpro software to formulate a GRADE summary of findings table (Supplementary Appendix 3) for each PICO question (34). The overall quality of evidence was evaluated using GRADE quality assessment criteria (31).

In clinical scenarios not addressed by data from randomized clinical trials, data from observational cohort studies were used to estimate relative effects. In situations in which the question had not been tested in a sample of patients taking GCs but had been tested in a non-GIOP population, we applied the relative risk values from that study, making the assumption that the effect was generalizable, but we downgraded the quality of evidence for indirectness.

We projected absolute risk reduction within each risk stratum according to hypothetical baseline fracture risk ranging from 1% to 20%. The following cut points were used to stratify levels of risk: <5% incidence of vertebral fractures over 5 years, between 5% and <10%, and ≥10%. The Voting Panel then made recommendations based on absolute fracture reduction with treatment in each of these strata. We focused on vertebral fracture rates because this outcome was more consistently reported in the literature and because of the greater effects of GCs on trabecular bone.

Moving from evidence to recommendations. GRADE methodology specifies that panels make recommendations based on the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the effect estimates), and patients' values and preferences. Key to the recommendation is the

Table 1. Fracture risk categories in GC-treated patients

	Adults ≥40 years of age	Adults <40 years of age
High fracture risk	Prior osteoporotic fracture(s) Hip or spine bone mineral density T score ≤−2.5 in men age ≥50 years and postmenopausal women FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ ≥20% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≥3%	Prior osteoporotic fracture(s)
Moderate fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ 10–19% FRAX* (GC-adjusted†) 10-year risk of hip fracture >1% and <3%	Hip or spine bone mineral density Z score <−3 **or** rapid bone loss (≥10% at the hip or spine over 1 year) **and** Continuing GC treatment at ≥7.5 mg/day for ≥6 months
Low fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ <10% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≤1%	None of above risk factors other than GC treatment

* https//www.shef.ac.uk/FRAX/tool.jsp.
† Increase the risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid (GC) treatment is >7.5 mg/day (e.g., if hip fracture risk is 2.0%, increase to 2.4%).
‡ Major osteoporotic fracture includes fractures of the spine (clinical), hip, wrist, or humerus.

tradeoff between desirable and undesirable outcomes and cost; recommendations require estimating the relative value patients place on the outcomes. We are unaware of published literature exploring patient values and preferences regarding these issues. Our judgments were based on the experience of the Panel members (which included a patient) in shared decision-making with their patients. Below we outline the Voting Panel's assessment of these tradeoffs that informed the final recommendations.

Consensus building. The Voting Panel voted on the direction and strength of the recommendation related to each PICO question. An 80% level of agreement was used as the threshold for a recommendation; if 80% agreement was not achieved during an initial vote, the Panel members held additional discussions before re-voting. Consistent with GRADE guidance, in some instances the Voting Panel chose to provide a strong recommendation despite a low quality rating of evidence (33). In such cases, a written explanation is provided, describing the reasons for this decision.

Moving from recommendations to practice. When applying these risk-stratified recommendations in clinical settings, adults ≥40 years of age receiving long-term GCs should be designated as being at moderate-to-high risk or low risk of fracture (Table 1) based on BMD, history of fracture, and 10-year risk of major OP fracture and hip fracture calculated using a tool that combines risk factors with GC dose. Although many tools that incorporate GC use are available, the Voting Panel suggested using FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) for fracture risk assessment. When GC use is included as a risk factor in FRAX, the fracture risk generated is the risk associated with a prednisolone dose of 2.5–7.5 mg/day (prednisolone and prednisone doses are nearly equivalent). For people receiving doses of >7.5 mg/day, the fracture risk generated with FRAX should be increased by a relative 15% for major osteoporotic fracture and 20% for hip fracture risk (13). For example, if the 10-year hip fracture risk is 2.0% with GC use entered in FRAX, the risk estimate should be increased to 2.4% if the prednisone dose is >7.5 mg.

There are no tools available to estimate absolute fracture risk in children or in adults <40 years of age. These groups were considered to be at high fracture risk if they have previously sustained an OP fracture. The Voting Panel designated men and women <40 years of age to be at moderate risk if they were expected to continue GC treatment at >7.5 mg/day for 6 months and had either 1) a hip or spine BMD Z score of <−3 or 2) a rapid decline in hip or spine BMD (equivalent to ≥10% in 1 year) during GC treatment.

RESULTS/RECOMMENDATIONS

How to interpret the recommendations

1. The Voting Panel's assessment was that patients would be willing to take calcium and vitamin D with only a very small absolute risk reduction, that all or virtually all would be willing to take bisphosphonates to achieve a 5-year absolute reduction in vertebral fracture risk of 5%, and that most would choose to take oral bisphosphonates if the fracture

reduction were ≥3% to <5% (leading to a conditional recommendation in favor). The 5-year time period was chosen because few clinical trials have data on fracture risk reduction past 3–5 years. Further, the Panel members thought that most patients would decline oral bisphosphonates with an absolute reduction in 5-year risk of vertebral fractures of 1.6–2.9% (leading to a conditional recommendation against), and all or virtually all would decline if the risk reduction were <1.5% (leading, in the presence of high- or moderate-quality evidence, to a strong recommendation against).

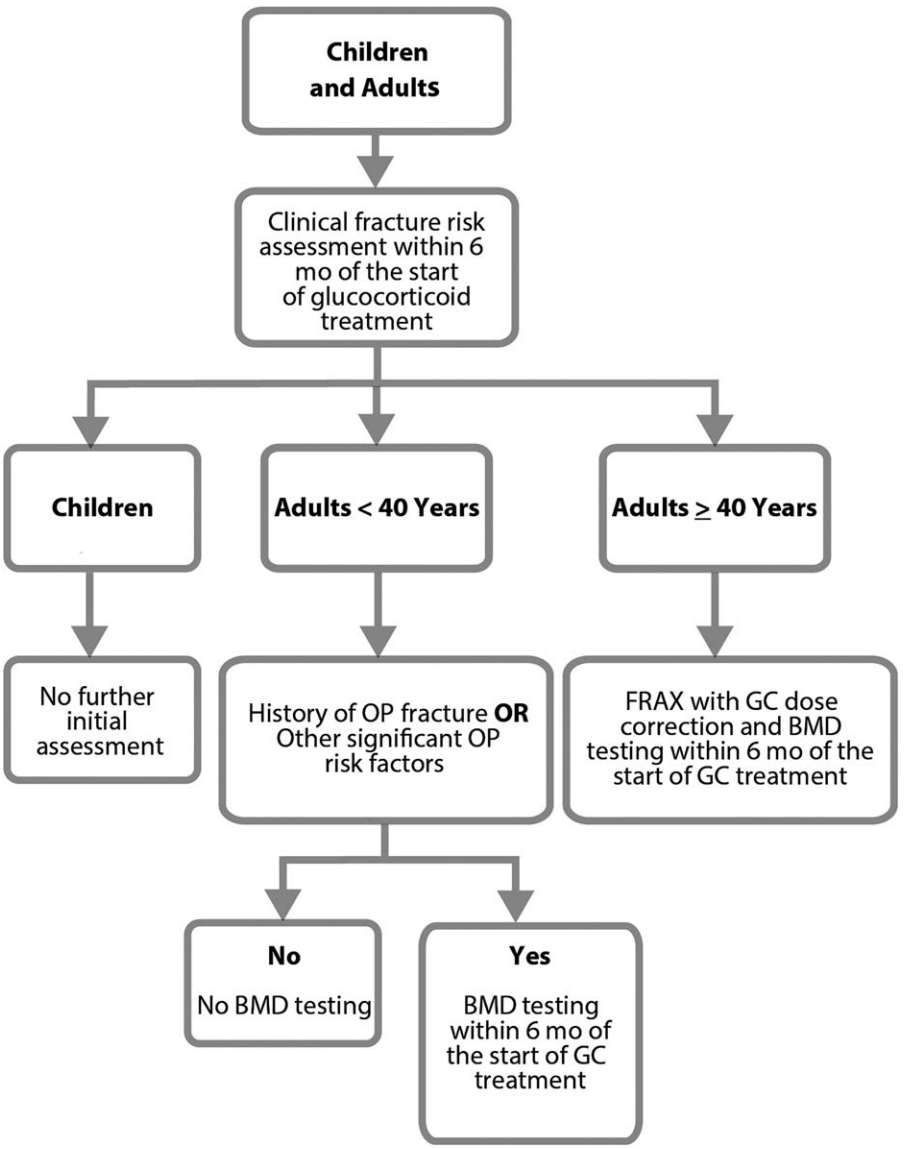
Children and Adults
Clinical fracture risk assessment within 6 mo of the start of glucocorticoid treatment
Children
Adults < 40 Years
Adults ≥ 40 Years
No further initial assessment
History of OP fracture OR Other significant OP risk factors
FRAX with GC dose correction and BMD testing within 6 mo of the start of GC treatment
No
No BMD testing
Yes
BMD testing within 6 mo of the start of GC treatment

Figure 1. Initial fracture risk assessment. A clinical fracture risk assessment includes obtaining a history with the details of glucocorticoid (GC) use (dose, duration, pattern of use), an evaluation for falls, fractures, frailty, and other osteoporosis (OP) risk factors (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use [at ≥3 units/day] or smoking) and other clinical comorbidities, and a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient's age. The risk of major osteoporotic fracture calculated with the FRAX tool (https://www.shef.ac.uk/FRAX/tool.jsp) should be increased by 1.15, and the risk of hip fracture by 1.2, if the prednisone dose is >7.5 mg/day (e.g., if the calculated hip fracture risk is 2.0%, increase to 2.4%). It is recognized that in some cases, bone mineral density (BMD) testing may not be available.

For intravenous (IV) bisphosphonates, denosumab, raloxifene, and teriparatide, which have greater harms or burden of treatment, the threshold was higher, although the Panel did not specify a threshold value. Because raloxifene may increase the risk of death due to stroke in postmenopausal women with documented coronary heart disease or at increased risk of major coronary events and/or may increase the risk of deep vein thrombosis and pulmonary embolism (35), and there is no evidence of its benefit in fracture reduction in GC-treated patients, the Voting Panel considered the drug as a treatment option only for postmenopausal women with contraindications to all other treatments. We are unaware of published literature exploring patient values and preferences regarding these issues. The judgments are based on the experience of the Panel members (which included a patient) in shared decision-making with their patients.

2a. A *strong recommendation* means that the Panel was *confident* that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion would not want to follow the recommendation.

2b. A *conditional recommendation* means that the Panel believed the desirable effects of following the recommendation *probably* outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach.

2c. A *good practice recommendation* (36) means that although the Panel believed the benefits of proceeding according to the guidance far outweigh the harms, the supporting evidence is indirect, and the Panel did not formally assess the relevant evidence. The logic for the good practice statements is as follows: Appropriate management regarding bone health is based on an initial assessment and reassessment of fracture risk. However, there are inadequate data directly addressing outcomes in patients whose cases were managed with, versus those without, initial and follow-up fracture risk assessments. The chain of evidence—limited antifracture treatment with limited adverse effects in those at low risk; more aggressive antifracture treatment with resultant decrease in fractures in those at high risk—is nevertheless compelling, though without a structured review of the evidence for the benefits and harms, the statement in question does not warrant a formal GRADE recommendation.

3. For each recommendation, details regarding the PICO questions and the GRADE evidence tables are listed in Supplementary Appendices 1 and 3 (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract).

4. Recommendations for BMD testing are based on the assumption that it is available in the region where the patient receives treatment and that there are no significant barriers, including the patient's functional status or financial barriers, that preclude testing, and that the results are likely to have an impact on clinical decision-making.

Recommendations for fracture risk assessment and reassessment

Initial fracture risk assessment. All of the fracture risk assessment and reassessment recommendations are made as good practice recommendations. In all adults and children, an *initial clinical fracture risk assessment should be performed as soon as possible, but at least within 6 months of the initiation of long-term GC treatment* (Figure 1). This assessment should include a history with the details of GC use (dose, duration, pattern of use), an evaluation for falls, fractures, frailty, and other risk factors for fracture (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use [at $\geq$3 units/day] or smoking) and other clinical comorbidities, and a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient's age.

In addition, for adults $\geq$40 years of age, the initial absolute fracture risk should be estimated using FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) with the adjustment for GC dose and BMD testing (if available, or without BMD if it is not available) as soon as possible, but at least within 6 months of the initiation of GC treatment.

For adults $<$40 years of age, BMD testing should be done as soon as possible but at least within 6 months of the initiation of GC treatment if the patient is at high fracture risk because of a history of previous OP fracture(s) or if the patient has other significant OP risk factors (malnutrition, significant

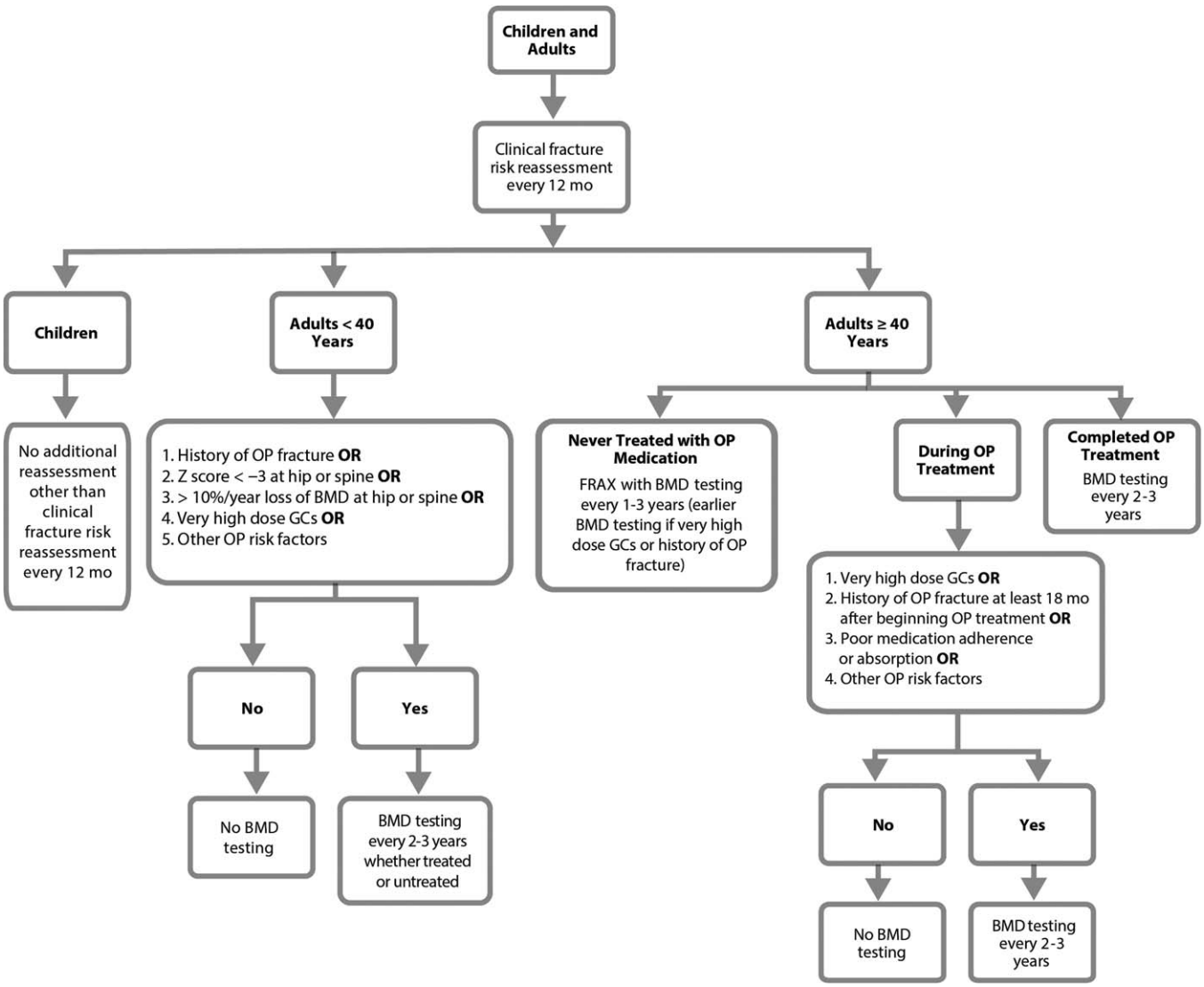
Children and Adults
Clinical fracture risk reassessment every 12 mo
Children
Adults < 40 Years
Adults ≥ 40 Years
No additional reassessment other than clinical fracture risk reassessment every 12 mo
1. History of OP fracture OR
2. Z score < −3 at hip or spine OR
3. > 10%/year loss of BMD at hip or spine OR
4. Very high dose GCs OR
5. Other OP risk factors
Never Treated with OP Medication
FRAX with BMD testing every 1-3 years (earlier BMD testing if very high dose GCs or history of OP fracture)
During OP Treatment
Completed OP Treatment
BMD testing every 2-3 years
1. Very high dose GCs OR
2. History of OP fracture at least 18 mo after beginning OP treatment OR
3. Poor medication adherence or absorption OR
4. Other OP risk factors
No
Yes
No BMD testing
BMD testing every 2-3 years whether treated or untreated
No
Yes
No BMD testing
BMD testing every 2-3 years

Figure 2. Reassessment of fracture risk. A clinical fracture risk reassessment includes obtaining a history with the details of glucocorticoid (GC) use (dose, duration, pattern of use), an evaluation for falls, fractures, frailty, and other osteoporosis (OP) risk factors (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use [at ≥3 units/day] or smoking) and other clinical comorbidities, and a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient's age. Very high-dose GC treatment was defined as treatment with prednisone ≥30 mg/day and a cumulative dose of >5 gm in the past year. Reliability of FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) after OP treatment is debated, but FRAX calculation can be repeated in adults age ≥40 years who have not received treatment. It is recognized that in some cases, bone mineral density (BMD) testing may not be available.

weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, smoking, alcohol use at ≥3 units/day).

Reassessment of fracture risk. In all adults and children who continue GC treatment, a *clinical fracture risk reassessment should be performed every 12 months* (Figure 2).

Adults ≥40 years of age. For adults ≥40 years of age who continue GC treatment and are *not treated with an OP medication beyond calcium and vitamin D,* reassessment with FRAX, with BMD testing if available,

Table 2. Recommendations for initial treatment for prevention of GIOP in adults (women not of child-bearing potential and men) beginning long-term GC treatment*

All adults taking prednisone at a dose of ≥2.5 mg/day for ≥3 months

Optimize calcium intake (1,000–1,200 mg/day)* **and vitamin D intake** (600–800 IU/day) **and lifestyle modifications** (balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to 1–2 alcoholic beverages/day) **over no treatment or over any of these treatments alone.**

Conditional recommendation because of indirect evidence on the impact of lifestyle modifications on fracture risk, low-quality evidence on the impact of calcium and vitamin D on fractures in GC users, and indirect evidence on the benefit of calcium and vitamin D on fracture risk in the general OP population

Adults age ≥40 years at low risk of fracture

Optimize calcium and vitamin D intake and lifestyle modifications over treatment with bisphosphonates, teriparatide, denosumab, or raloxifene.

Conditional recommendation for calcium and vitamin D over oral bisphosphonates, teriparatide, and denosumab because of low-quality evidence on additional antifracture benefit of the alternative treatments in this low-risk group, costs, and potential harms

Strong recommendation for calcium and vitamin D over IV bisphosphonates and raloxifene because of low-quality evidence on additional antifracture benefit in this low-risk group and their potential harms

Adults age ≥40 years at moderate risk of major fracture

Treat with an oral bisphosphonate over calcium and vitamin D alone.

Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, denosumab, or raloxifene.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications.
Other therapies if oral bisphosphonates are not appropriate, in order of preference:
- IV bisphosphonates
  - Higher risk profile for IV infusion over oral bisphosphonate therapy
- Teriparatide
  - Cost and burden of therapy with daily injections
- Denosumab
  - Lack of safety data in people treated with immunosuppressive agents
- Raloxifene (for postmenopausal women in whom none of the medications listed above is appropriate)
  - Lack of adequate data on benefits (impact on risk of vertebral and hip fractures in GC users) and potential harms (clotting risks, mortality)

Conditional recommendations because of indirect and low-quality evidence comparing benefits and harms of alternative treatments in people with moderate fracture risk

Adults age ≥40 years at high risk of fracture

Treat with an oral bisphosphonate over calcium and vitamin D alone.

Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, denosumab, or raloxifene.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications.
Other therapies if oral bisphosphonates are not appropriate, in order of preference:
- IV bisphosphonates
  - Higher risk profile for IV infusion over oral bisphosphonate therapy
- Teriparatide
  - Cost and burden of therapy with daily injections
- Denosumab
  - Lack of safety data in people treated with immunosuppressive agents
- Raloxifene (for postmenopausal women in whom none of the medications listed above is appropriate)
  - Lack of adequate data on benefits (impact on risk of vertebral and hip fractures in GC users) and potential harms (clotting risks, mortality)

Strong recommendation for oral bisphosphonates over calcium and vitamin D alone because of the strength of the indirect evidence of antifracture efficacy and low harms

All other recommendations **conditional** because of indirect and low-quality evidence comparing benefits and harms of alternative treatments in people with high fracture risk

Adults age <40 years at low risk of fracture

Optimize calcium and vitamin D intake and lifestyle modifications over treatment with bisphosphonates, teriparatide, or denosumab.

Conditional recommendation for calcium and vitamin D over oral bisphosphonates, teriparatide, and denosumab because of low-quality evidence on additional antifracture benefit of the alternative treatments, costs, and potential harms

Strong recommendation for calcium and vitamin D over IV bisphosphonates because of low-quality evidence for additional antifracture benefit in this low-risk group and potential harms

*Correction added after online publication 27 September 2017: the dosage for optimized calcium intake has been changed from 800–1,000 mg/day to 1,000–1,200 mg/day.

Table 2. *(Cont'd)*

Adults age <40 years at moderate-to-high risk of fracture
Treat with an oral bisphosphonate over calcium and vitamin D alone.
Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, or denosumab.
Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications. Other therapies if oral bisphosphonates are not appropriate, in order of preference: IV bisphosphonates Higher risk profile for IV infusion over oral bisphosphonate therapy Teriparatide Cost and burden of therapy with daily injections Denosumab Lack of safety data in people treated with immunosuppressive agents
Conditional recommendations because of low- to very low-quality evidence on absolute fracture risk and indirect and low-quality evidence comparing relative harms and benefits of alternative treatments in this age group

* GIOP = glucocorticoid (GC)–induced osteoporosis; IV = intravenous.

should be completed every 1–3 years. This reassessment should be performed earlier within this 1–3-year time range for adults age ≥40 years who are receiving very high doses of GCs (initial prednisone dose ≥30 mg/day, cumulative dose >5 gm in the previous year) or those with a history of OP fracture(s). Later or less frequent testing within this range can be done for adults age ≥40 years who are taking lower doses of GCs with no other OP risk factors.

For adults ≥40 years old who continue GC treatment and are *currently treated with an OP medication in addition to calcium and vitamin D*, BMD testing should be completed every 2–3 years during treatment in high-risk patients such as those receiving very high-dose GCs (initial prednisone dose ≥30 mg/day, cumulative dose >5 gm in the previous year), a history of OP fracture occurring after ≥18 months of treatment with antifracture medication (other than calcium and vitamin D), risks for poor medication adherence or absorption, or other significant OP risk factors.

For adults ≥40 years old who *received an OP treatment in the past but are no longer being treated with an OP medication other than calcium and vitamin D,* BMD testing should be done every 2–3 years. Within this range, reassessment should be conducted earlier in patients receiving higher doses of GCs and those with a history of fracture or low BMD, and later in those receiving lower doses of GCs, with higher BMD and no other OP risk factors.

Adults <40 years of age. For all adults <40 years of age who continue GC treatment and are *at moderate-to-high fracture risk* (history of previous fracture, BMD Z score <−3, received very high-dose prednisone [≥30 mg/day and cumulative dose >5 gm] in the previous year, risks for poor medication adherence or absorption, or multiple OP risk factors), BMD testing should be done every 2–3 years.

Recommendations for treatment

The Voting Panel's rationale and strength of recommendations for treatment are detailed in Table 2.

Calcium and vitamin D intake and lifestyle modifications. Optimizing calcium intake (1,000–1,200 mg/day) and vitamin D intake (600–800 IU/day; serum level ≥20 ng/ml) (37) as well as lifestyle modifications (a balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to 1–2 alcoholic beverages/day) are conditionally recommended for all patients receiving GC treatment.

Initial pharmacologic treatment. *Adults ≥40 years of age.* Women ≥40 years of age and not of childbearing potential and men ≥40 years of age (Figure 3) who are at moderate-to-high risk of fracture should be treated with an oral bisphosphonate (strong recommendation for those at high risk; conditional recommendation for those at moderate risk). For patients in whom oral bisphosphonates are not appropriate (for example, due to comorbidities, patient preference, or concerns about adherence with an oral medication regimen), IV bisphosphonates should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If bisphosphonate treatment is not appropriate, teriparatide should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If neither oral nor IV bisphosphonates nor teriparatide treatment is appropriate, denosumab should be used rather than the patient receiving no additional treatment beyond calcium and

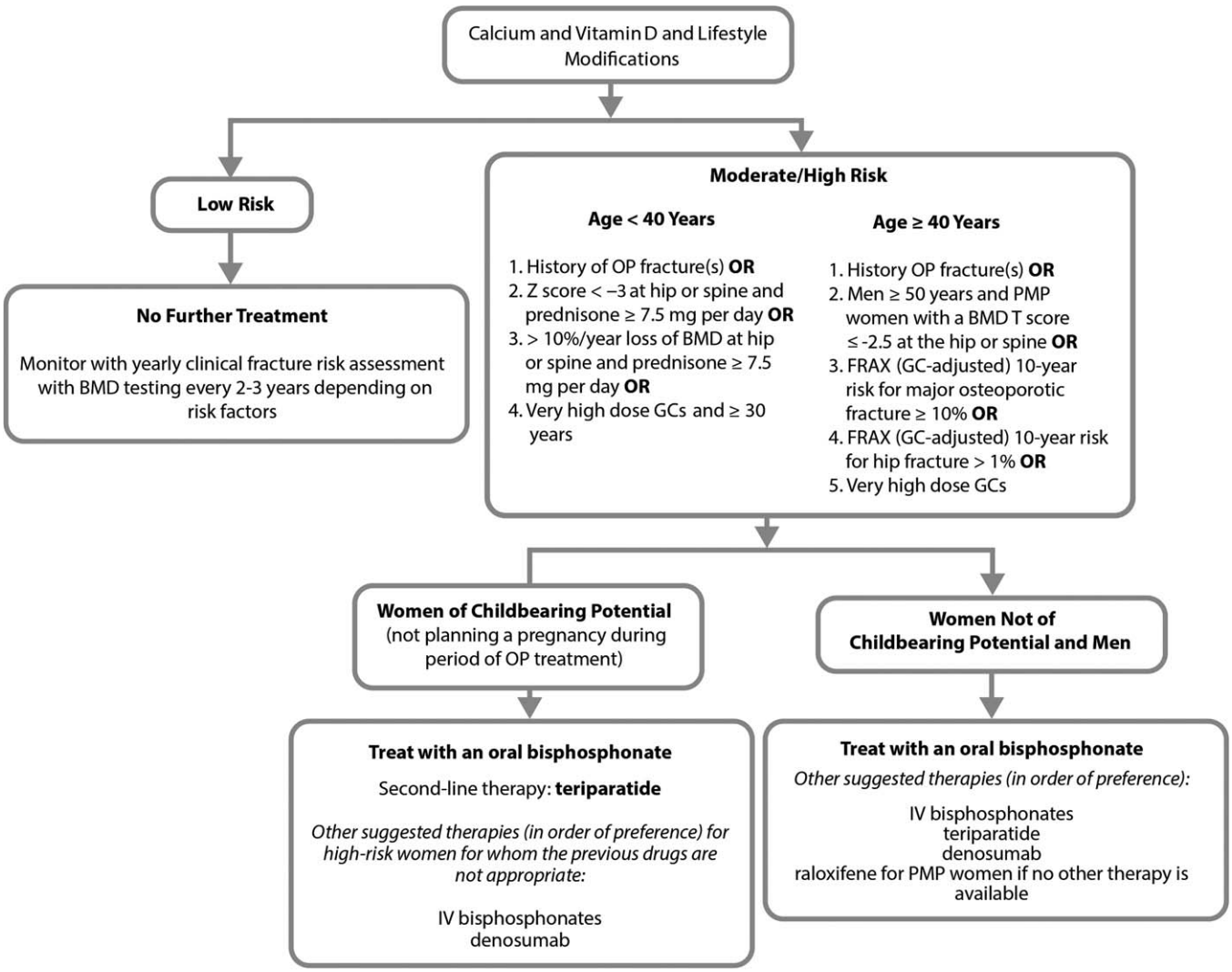
Calcium and Vitamin D and Lifestyle Modifications
Low Risk
No Further Treatment
Monitor with yearly clinical fracture risk assessment with BMD testing every 2-3 years depending on risk factors
Moderate/High Risk
Age < 40 Years
1. History of OP fracture(s) OR
2. Z score < –3 at hip or spine and prednisone ≥ 7.5 mg per day OR
3. > 10%/year loss of BMD at hip or spine and prednisone ≥ 7.5 mg per day OR
4. Very high dose GCs and ≥ 30 years
Age ≥ 40 Years
1. History OP fracture(s) OR
2. Men ≥ 50 years and PMP women with a BMD T score ≤ -2.5 at the hip or spine OR
3. FRAX (GC-adjusted) 10-year risk for major osteoporotic fracture ≥ 10% OR
4. FRAX (GC-adjusted) 10-year risk for hip fracture > 1% OR
5. Very high dose GCs
Women of Childbearing Potential (not planning a pregnancy during period of OP treatment)
Women Not of Childbearing Potential and Men
Treat with an oral bisphosphonate
Second-line therapy: teriparatide
Other suggested therapies (in order of preference) for high-risk women for whom the previous drugs are not appropriate:
IV bisphosphonates
denosumab
Treat with an oral bisphosphonate
Other suggested therapies (in order of preference):
IV bisphosphonates
teriparatide
denosumab
raloxifene for PMP women if no other therapy is available

Figure 3. Initial pharmacologic treatment for adults. Recommended doses of calcium and vitamin D are 1,000–1,200 mg/day and 600–800 IU/day (serum level ≥20 ng/ml), respectively. Lifestyle modifications include a balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing and resistance training exercise, and limiting alcohol intake to 1–2 alcoholic beverages/day. Very high-dose glucocorticoid (GC) treatment was defined as treatment with prednisone ≥30 mg/day and a cumulative dose of >5 gm in the past year. The risk of major osteoporotic (OP) fracture calculated with the FRAX tool (https://www.shef.ac.uk/FRAX/tool.jsp) should be increased by 1.15, and the risk of hip fracture by 1.2, if the prednisone dose is >7.5 mg/day (e.g., if the calculated hip fracture risk is 2.0%, increase to 2.4%). It is recognized that in some cases, bone mineral density (BMD) testing may not be available. PMP = postmenopausal; IV = intravenous.

vitamin D. For postmenopausal women in whom none of these medications is appropriate, raloxifene should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. The order of the preferred treatments was determined based on a comparison of efficacy (fracture reduction), toxicity, and cost. These are conditional recommendations.

Adults <40 years of age. For adults <40 years of age (women not of childbearing potential and men) (Figure 3) with a history of OP fracture, or those continuing GC treatment (≥6 months at a dose of ≥7.5 mg/day) who have either a hip or spine BMD Z score < -3 or bone loss of ≥10%/year at the hip or spine as assessed by dual x-ray absorptiometry (DXA), an oral bisphosphonate should

Table 3. Recommendations for initial treatment for prevention of GIOP in special populations of patients beginning long-term GC treatment*

Women of childbearing potential at moderate-to-high risk of fracture (Table 1) who do not plan to become pregnant within the period of OP treatment and are using effective birth control or are not sexually active

Treat with an oral bisphosphonate over calcium and vitamin D alone, teriparatide, IV bisphosphonates, or denosumab.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications.
Other therapies if oral bisphosphonates are not appropriate, in order of preference:
- Teriparatide
  - Safety, cost, and burden of therapy with daily injections

Consider the following therapies only for **high-risk** patients because of lack of safety data on use of these agents during pregnancy:
- IV bisphosphonates
  - Potential fetal risks of IV infusion during pregnancy
- Denosumab
  - Potential fetal risks during pregnancy

Conditional recommendations because of indirect and very low-quality evidence on benefits and harms of these treatments to the fetus during pregnancy

Adults age ≥30 years receiving very high-dose GCs (initial dose of prednisone ≥30 mg/day and cumulative dose >5 gm in 1 year)

Treat with an oral bisphosphonate over calcium and vitamin D alone.

Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, or denosumab.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of additional antifracture benefits from other OP medications.

If bisphosphonate treatment is not appropriate, alternative treatments are listed by age (≥40 years and <40 years) in Table 2.

Conditional recommendations because of low-quality evidence on absolute fracture risk and harms in this population

Adults with organ transplant, glomerular filtration rate ≥30 ml/minute, and no evidence of metabolic bone disease who continue treatment with GCs

Treat according to the age-related guidelines for adults without transplants (Table 2), with these additional recommendations:

An evaluation by an expert in metabolic bone disease is recommended for all patients with a renal transplant.

Recommendation against treatment with denosumab due to lack of adequate safety data on infections in adults treated with multiple immunosuppressive agents.

Conditional recommendations because of low-quality evidence on antifracture efficacy in transplant recipients and on relative benefits and harms of the alternative treatments in this population

Children ages 4–17 years treated with GCs for ≥3 months

Optimize calcium intake (1,000 mg/day) and vitamin D intake (600 IU/day) and lifestyle modifications over not optimizing calcium and vitamin D intake and lifestyle modifications.

Conditional recommendation because of lack of antifracture efficacy of calcium and vitamin D in children but limited harms

Children ages 4–17 years with an osteoporotic fracture who are continuing treatment with GCs at a dose of ≥0.1 mg/kg/day for ≥3 months

Treat with an oral bisphosphonate (IV bisphosphonate if oral treatment contraindicated) plus calcium and vitamin D over treatment with calcium and vitamin D alone.

Conditional recommendation because of very low-quality antifracture data in children but moderate-quality evidence of low harms of oral bisphosphonates in children and less potential harm of oral over IV bisphosphonates

* GIOP = glucocorticoid (GC)–induced osteoporosis; IV = intravenous.

be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If treatment with an oral bisphosphonate is not appropriate, the same alternative medications listed for adults ≥40 years of age are recommended with the exception of raloxifene, which is not used in men and premenopausal women. These are conditional recommendations.

Special populations. For women who meet criteria for *moderate-to-high risk of fracture* (Table 1) and are of *childbearing potential* (Table 3 and Figure 3), *but do not plan to become pregnant within the period of OP treatment and are using effective birth control or are not sexually active,* an oral bisphosphonate should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If oral bisphosphonate treatment is not appropriate, teriparatide should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. Because of the lack of safety data and the potential fetal harm associated with denosumab in animal studies and with high-dose IV bisphosphonates (38–53), these therapies should be used only in women who are at high risk of fracture in whom treatment with an oral bisphosphonate and teriparatide is not appropriate. Denosumab or IV bisphosphonate treatment should be initiated only after a discussion with the patient about the very low quality of evidence about fetal harms in the event of an unplanned pregnancy. These are conditional recommendations.

There is a lack of data on the safety of currently available OP treatments during pregnancy. Therefore, these guidelines do not include recommendations about OP prevention or treatment, other than calcium and vitamin D intake and lifestyle modification, in women who are pregnant.

For *adults ≥30 years of age who are receiving very high-dose GC treatment* (initial prednisone dose of ≥30 mg/day [or equivalent GC exposure] and a cumulative annual dose of >5 gm) (Table 3), oral bisphosphonate treatment should be initiated. If treatment with an oral bisphosphonate is not appropriate, the age-related recommendations for second-line therapy (Table 2) should be followed (with adjustments for women of childbearing potential as outlined in these guidelines). These are conditional recommendations.

For adults *who have received an organ transplant and who are continuing treatment with GCs* (Table 3),

Table 4. Recommendations for follow-up treatment for prevention of GIOP*

Adults age ≥40 years continuing GC treatment who have had a fracture that occurred after ≥18 months of treatment with an oral bisphosphonate or who have had a significant loss of bone mineral density (≥10%/year)

Treat with another class of OP medication (teriparatide or denosumab; or, consider IV bisphosphonate if treatment failure is judged to be due to poor absorption or poor medication adherence) with calcium and vitamin D over calcium and vitamin D alone or over calcium and vitamin D and continued oral bisphosphonate.

Conditional recommendation because of very low-quality evidence comparing benefits and harms of the compared treatment options in this clinical situation

Adults age ≥40 years who have completed 5 years of oral bisphosphonate treatment and who continue GC treatment and are assessed to be at moderate-to-high risk of fracture

Continue active treatment (with an oral bisphosphonate beyond 5 years or switch to IV bisphosphonate [if concern with regard to adherence or absorption] or switch to an OP treatment in another class) over calcium and vitamin D alone.

Conditional recommendation because of very low-quality data on benefits and harms in GC-treated patients, but moderate-quality data in the general OP literature on benefits and harms of continuing treatment with oral bisphosphonates past 5 years for people at high risk of fracture

Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at low risk of fracture

Discontinue the OP medication but continue calcium and vitamin D over continuing the OP medication.

Conditional recommendation made by expert consensus; evidence informing it too indirect for the population and very low-quality

Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at moderate-to-high risk of fracture

Complete the treatment with the OP medication over discontinuing the OP medication.

Strong recommendation for high-risk patients based on expert consensus that patients who are at high risk should continue an OP treatment in addition to calcium and vitamin D

Conditional recommendation for moderate-risk patients because of lower fracture risk compared to potential harms

* GIOP = glucocorticoid (GC)–induced osteoporosis; IV = intravenous.

the age-related treatment recommendations outlined in these guidelines for men and women who do not have transplants should be followed if the glomerular filtration rate is ≥30 ml/minute and there is no evidence of metabolic bone disease. An evaluation by an expert in metabolic bone disease is recommended before initiating pharmacologic treatment in adults with a renal transplant (54). The Panel made a recommendation against the use of denosumab because of lack of safety data in this population of patients who are treated with multiple immunosuppressive agents. These are conditional recommendations.

For *GC-treated children 4–17 years of age,* a calcium intake of 1,000 mg/day and vitamin D intake of 600 IU/day is recommended. For children who have had an OP fracture who continue GC treatment at a dose of ≥0.1 mg/kg/day for ≥3 months, treatment with an oral bisphosphonate (or an IV bisphosphonate if oral treatment is not appropriate) is recommended (Table 3). These are conditional recommendations.

Follow-up treatment recommendations. *Initial treatment failure.* For adults ≥40 years of age who are continuing GC treatment who have had a fracture that occurred ≥18 months after beginning treatment with an oral bisphosphonate or had a significant decline in BMD (≥10%/year) after 1 year of treatment (Table 4), treatment with another class of OP medication (teriparatide, denosumab) or an IV bisphosphonate (if treatment failure is judged to be due to poor absorption or poor medication adherence) is recommended rather than the patient receiving no additional treatment beyond calcium and vitamin D alone or continuing oral bisphosphonate treatment. These are conditional recommendations.

Treatment if moderate-to-high fracture risk persists after bisphosphonate therapy. For adults ≥40 years of age who have completed 5 years of oral bisphosphonate treatment (Table 4) who are continuing GC treatment and are assessed to be at moderate-to-high risk of fracture (Table 1), continuation of active OP treatment (in addition to calcium and vitamin D) is recommended rather than the patient receiving no additional treatment beyond calcium and vitamin D. Suggested treatment options include continuing the oral bisphosphonate for 7–10 years, switching to an IV bisphosphonate if absorption or adherence is a problem, or treatment with another class of OP medication (teriparatide or denosumab), depending on the response to the initial bisphosphonate treatment (change in BMD, new fractures) and with consideration of rare risks, including jaw necrosis and atypical femur fractures, which might increase with the duration of antiresorptive therapy. These are conditional recommendations.

Treatment if GCs are discontinued. For adults ≥40 years of age who are treated with OP medication in addition to calcium and vitamin D and are discontinuing GC treatment (Table 4), discontinuation of the OP medication is recommended if fracture risk at the time of GC discontinuation is assessed to be low. Otherwise, the OP treatment course should be completed or continued until the fracture risk is assessed to be low. Continuation of OP treatment in the setting of high risk is a strong recommendation. The others are conditional recommendations.

Application of these treatment recommendations. These recommendations are made for average or typical GC-treated patients. They may not be applicable to GC-treated patients with multiple risk factors or feasible for patients with financial or social barriers to testing and treatment.

DISCUSSION

This report presents the updated ACR recommendations for the prevention and treatment of osteoporosis and fractures in patients receiving glucocorticoid treatment. The goal is to optimize identification of patients at risk of GC-induced fractures so that they can be appropriately treated while limiting the risk and the burden of testing and treatment. The guiding principle for these guidelines was to use outcome measures that are clinically relevant to patients and providers, so in decision-making, data about absolute fracture risk reduction were given priority over BMD changes. The recommendations on the order of first-line treatments were based on the Voting Panel's assessment of antifracture efficacy, potential harms, and costs. Thus, oral bisphosphonates were recommended as the preferred first-line therapy in most clinical situations given their antifracture benefit, safety, and low cost, unless there are contraindications, intolerance, or concerns about patient adherence to treatment.

Robust methodology was used in the literature search. The Voting Panel had a broad representation of clinicians, both primary care providers and subspecialists, with experience in bone health and in prescribing GC medications. In addition, these guidelines include recommendations for the assessment and reassessment of fracture risk and antifracture therapy during GC treatment and for special populations, such as children, people with organ transplants, people receiving very high doses of GCs, and women of childbearing potential.

There are limitations to these recommendations. First, many important clinical situations could not be addressed given the limited scope of this guideline

project. Recommendations addressing initial assessment and reassessment of fracture risk were made as good practice recommendations (36) because, although the Panel believes that the benefits of proceeding according to the guidance far outweigh the undesirable consequences, the supporting evidence is indirect or not available, and the Panel did not formally gather, summarize, or assess the relevant evidence.

We adopted generally accepted thresholds to define high, medium, and low levels of absolute risk of incident fracture (i.e., <10%, 10–19%, and ≥20% 10-year risk of major osteoporotic fracture). These cut points were used to stratify PICO questions and weigh potential benefits versus harms in those different clinical situations. However, the application of these recommendations to a clinical setting requires that the physician assign the individual patient into a risk stratum. For adults age ≥40 years, this can be accomplished using fracture risk calculators that take the GC dose into account, such as the FRAX tool. However, FRAX has important limitations. First, the fracture risk generated when GC use is included as a risk factor estimates the risk that would be associated with moderate-dose prednisone (2.5–7.5 mg/day). To accurately estimate the risk associated with doses of >7.5 mg/day, the clinician must multiply the risk of major osteoporotic fracture and the risk of hip fracture generated with the FRAX by 1.15 and by 1.2, respectively. This adjustment may not adequately estimate the risk associated with very high-dose GC use. FRAX uses hip BMD to calculate fracture risk, but GC use has a greater impact on spine BMD. For GC-treated patients with discordant spine and hip BMD (with lower spine BMD), the Fracture Risk Calculator, which includes spine BMD in absolute fracture risk estimation, is available (https://riskcalculator.fore.org). Finally, there is debate about the validity of FRAX fracture risk estimates after pharmacologic treatment for OP, which should be considered in the reassessment of fracture risk in treated patients.

The available evidence about fracture risk and risk reduction was particularly limited with regard to treatment recommendations in adults <40 years of age and children, and there are no tools available to estimate absolute fracture risk in these age groups. Younger people are often treated with higher doses of GCs, but they have higher bone mass and greater potential for recovery of bone mass when the GC treatment is discontinued. To try to better categorize fracture risk in adults <40 years of age, the Panel considered several risk factors as indicators of moderate-to-high fracture risk—including history of previous fragility fracture, significant decrease in BMD, or low BMD Z score with continued use of prednisone (limiting the recovery of bone mass) at a dose of ≥7.5 mg/day for at least 6 months—in patients <40 years old, as well as in patients ≥30 years old treated with very high doses of GCs (initial prednisone dose ≥30 mg/day with a cumulative dose of >5 gm) (15,18,21–25). The lack of data on long-term outcomes with OP treatment in this age group may lead to under- or overtreatment, but the possible benefits to long-term bone health and the relatively low risks associated with the recommended OP treatments led to the recommendation of treatment with an oral bisphosphonate in addition to calcium and vitamin D. There is a need for more research about absolute risk of fracture in this age group during and after GC use and into later adult life.

Fracture data are very limited in GIOP-specific clinical trials and population studies. Lacking these data, the relative fracture reduction associated with OP medications was extrapolated from the risk reduction ascertained in clinical trials of many different treatments for OP in general. While this step introduced indirectness into the quality of evidence for many PICO questions, it is reassuring that where parallel data from GIOP and non-GIOP trials exist, the derived relative risks for treatment effects from the same intervention are often similar, indicating that the assumption of generalizability may be reasonable (Supplementary Appendix 3 [Summary of Findings Tables 1.4a/b/c, 1.9a/b/c], available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract). Imprecision in the estimate of benefits of treatment is increased by these extrapolations. Future clinical trials in GC-treated patients should include fracture as a primary outcome measure.

The Panel faced low-quality evidence regarding the magnitude of benefit GC-treated patients would require as a tradeoff for assuming the burden and risks of treatment for lowering fracture risk, particularly given the uncertainties associated with estimates of benefit. Awareness of the need to attain "minimally disruptive medicine" (55) has increased in recent years, and many of the candidate patients already bear the burden of multiple medications. This burden may influence their willingness to tolerate yet additional treatment. The Panel's assessment was that patients would be willing to take calcium and vitamin D with only a very small absolute risk reduction, that all or virtually all would be willing to take bisphosphonates to achieve a 5-year absolute reduction in vertebral fracture risk of 5%, and that most would choose to take oral bisphosphonates if the fracture reduction were between ≥3% and <5%. Patients who value these small absolute reductions less

highly than the Panel estimated may decide against recommended treatment after discussion of risks and benefits with their providers.

There are concerns about the potential harms of calcium and vitamin D supplementation with regard to cardiovascular risks (56,57). Optimizing calcium intake, however, may be even more important in GC-treated patients because of the increase in urinary calcium excretion during GC use. For this reason, the guidelines suggest optimizing dietary intake of calcium. More research about the benefits and harms of supplemental calcium and vitamin D in GC-treated patients is needed.

Because of these limitations, most of the recommendations in this guideline are conditional or good clinical practice recommendations. Further studies are needed to examine differences in fracture risk in people with different OP risk factors (age, race, and sex), the role of spine imaging using vertebral fracture assessment with DXA or radiography in assessing fracture risk in GC users, the risk of OP medications to the fetus in women of childbearing potential, and the impact of OP treatment versus no treatment on adult bone health and fracture risk in GC-treated children.

GIOP is not a problem that is unique to rheumatology; GCs are widely prescribed by primary care providers and subspecialists. The Panel's judgments regarding patients' values and preferences were informed by input from the primary care physicians, non-rheumatology specialists, and the patient who served on the Panel. This patient highlighted the significant challenges that patients and clinicians confront when making decisions about optimizing bone health during GC treatment of chronic inflammatory conditions.

ACKNOWLEDGMENTS

We thank Jonathan (Rick) Adachi, MD, Robert Adler, MD, Marcy Bolster, MD, Roberto Civitelli, MD, Jeffrey Curtis, MD, MPH, Chad Deal, MD, Michael Maricic, MD, Clifford Rosen, MD, Kenneth Saag, MD, MSc, Emily von Scheven, MD, and Barton Wise, MD for serving on the Expert Panel. We thank Tom Nickolas, MD, MS, and Elizabeth Shane, MD for providing expert advice. We thank the Arthritis Foundation for its assistance with patient involvement in this guideline project, as well as the patients who participated in this project. We thank the ACR staff, including Ms Regina Parker for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, Ms Robin Lane for assistance in manuscript preparation, and Ms Lauren Evans for assistance throughout the literature review process. We thank Ms Janet Joyce for help in developing the literature search strategy and performing the literature search and updates, and Ms Tamara Radar for peer reviewing the literature search strategy.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Buckley had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Buckley, Guyatt, Fink, Cannon, Grossman, Hansen, Humphrey, Lane, Magrey, M. Miller, Morrison, Rao, Robinson, Saha, Wolver, Bannuru, Vaysbrot, Osani, Turgunbaev, A. S. Miller, McAlindon.

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Analysis and interpretation of data. Buckley, Guyatt, Fink, Cannon, Grossman, Hansen, Humphrey, Lane, Magrey, M. Miller, Morrison, Rao, Robinson, Saha, Wolver, Bannuru, Vaysbrot, Osani, Turgunbaev, A. S. Miller, McAlindon.

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Sjogren syndrome

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EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies

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Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2019-216114).

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Received 31 July 2019
Revised 2 October 2019
Accepted 2 October 2019
Published Online First 31 October 2019

Check for updates

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To cite: Ramos-Casals M, Brito-Zerón P, Bombardieri S, *et al*. *Ann Rheum Dis* 2020;**79**:3–18.

ABSTRACT

The therapeutic management of Sjögren syndrome (SjS) has not changed substantially in recent decades: treatment decisions remain challenging in clinical practice, without a specific therapeutic target beyond the relief of symptoms as the most important goal. In view of this scenario, the European League Against Rheumatism (EULAR) promoted and supported an international collaborative study (EULAR SS Task Force) aimed at developing the first EULAR evidence and consensus-based recommendations for the management of patients with SjS with topical and systemic medications. The aim was to develop a rational therapeutic approach to SjS patients useful for healthcare professionals, physicians undergoing specialist training, medical students, the pharmaceutical industry and drug regulatory organisations following the 2014 EULAR standardised operating procedures. The Task Force (TF) included specialists in rheumatology, internal medicine, oral health, ophthalmology, gynaecology, dermatology and epidemiology, statisticians, general practitioners, nurses and patient representatives from 30 countries of the 5 continents. Evidence was collected from studies including primary SjS patients fulfilling the 2002/2016 criteria; when no evidence was available, evidence from studies including associated SjS or patients fulfilling previous sets of criteria was considered and extrapolated. The TF endorsed the presentation of general principles for the management of patients with SjS as three overarching, general consensus-based recommendations and 12 specific recommendations that form a logical sequence, starting with the management of the central triplet of symptoms (dryness, fatigue and pain) followed by the management of systemic disease. The recommendations address the use of topical oral (saliva substitutes) and ocular (artificial tear drops, topical non-steroidal anti-inflammatory drugs, topical corticosteroids, topical CyA, serum tear drops) therapies, oral muscarinic agonists (pilocarpine, cevimeline), hydroxychloroquine, oral glucocorticoids, synthetic immunosuppressive agents (cyclophosphamide, azathioprine, methotrexate, leflunomide and mycophenolate), and biological therapies (rituximab, abatacept and belimumab). For each recommendation, levels of evidence (mostly modest) and TF agreement (mostly very high) are provided. The 2019 EULAR recommendations are based on the evidence collected in the last 16 years in the management of primary 2002 SjS patients and on discussions between a large and broadly international TF. The recommendations synthesise current thinking on SjS treatment in a set of overarching principles and recommendations. We hope that the current recommendations will be broadly applied in clinical practice and/or serve as a template for national societies to develop local recommendations.

INTRODUCTION

Sjögren syndrome (SjS), a systemic autoimmune disease that affects 1–23 persons per 10 000 inhabitants in European countries,[1] presents with a wide spectrum of clinical manifestations and autoantibodies. Antinuclear antibodies are the most frequently detected autoantibodies, anti-Ro/SS-A the most specific, and cryoglobulins and hypocomplementaemia the main prognostic markers.[2] The histological hallmark is a focal infiltration of the exocrine glands by lymphocytes, determined by minor labial salivary gland biopsy. The clinical scenario is dominated by sicca syndrome caused by immune-mediated glandular involvement, accompanied by fatigue, musculoskeletal pain and systemic features in a significant percentage of patients, and complicated by lymphoma in around 2%–5% of patients.[3] When SjS appears in a previously healthy person, the disease is classified as primary, while patients with concomitant systemic autoimmune diseases (SAD) are classified as associated (or secondary) SjS; since this distinction only reflects a clinical situation of autoimmune coexistence the term SjS will be throughout the manuscript. SjS patients make substantial use of healthcare services, with a mean annual total direct cost per patient ranging between £2200 in UK and US$20 000 in the USA.[4 5]

The therapeutic management of SjS has not changed substantially in recent decades[6] and is still based on symptomatic treatment of sicca

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symptomatology and broad-spectrum immunosuppression for systemic disease, with insufficient information on the differential efficacy and safety of the therapeutic options available.[7] Treatment decisions remain challenging in clinical practice, without a specific therapeutic target beyond the relief of symptoms as the most important goal. Therefore there is growing interest in the proposal of clinical guidelines by national scientific societies.[8–11]

In 2010, the European League Against Rheumatism (EULAR) promoted and supported an international collaborative study (EULAR SS Task Force) aimed at developing disease-specific activity indexes in SjS (EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and EULAR Sjögren's syndrome disease activity index (ESSDAI) scores),[12 13] which are now widely used both clinically and in research. A second project, the development of the first EULAR evidence and consensus-based recommendations for the management of patients with SjS with topical and systemic medications, was proposed and launched.

METHODS

After approval of the proposal by the EULAR Executive Committee, the convenor (MR-C) and co-convenors (CV, SB, XM) invited international experts with a solid history of clinical research in SjS (most of whom were previously involved in the ESSDAI/ESSPRI project) to form part of a Steering Committee (SC) and a Task Force (TF), which also included methodologists, patient representatives and individuals from all relevant professional groups (online supplementary appendix 1). The aim was to develop a rational therapeutic approach to SjS patients that would be useful for healthcare professionals, doctors in specialist training, medical students, the pharmaceutical industry and drug regulatory organisations following the 2014 EULAR standardised operating procedures.[14] Industry involvement was not permitted at any stage of the project.

Steering committee

The SC included 13 rheumatologists, four internal medicine, one primary care and one oral health specialists, one epidemiologist, one statistician, one healthcare professional representative and two patient representatives. The SC agreed on some principal considerations upfront: (a) The statements were termed 'recommendations' as opposed to 'guidelines' or 'points to consider' because they offer guidance, which needs to be tailored to meet individual requirements. (b) Some general rules and definitions (overarching principles, general recommendations, definition of sequential therapeutic schedules, severity or refractoriness) cannot be evidence-based and were, therefore based on consensus. (c) The remaining statements were evidence-based, that is, supported by the highest level of evidence possible, limiting statements based only on retrospective data (although for some clinical or therapeutic scenarios with no data in controlled studies, this was allowed if the amount of retrospective data was considered significant and scientifically reliable); recommendations based on data obtained from case reports were not allowed. (d) Evidence was collected from studies including primary SjS patients fulfilling the 2002/2016 criteria (SjS-2002).[15 16] When no evidence was available, evidence from studies including associated SjS, patients fulfilling previous sets of criteria or those including a mix of autoimmune and non-autoimmune aetiologies was considered and extrapolated (online supplementary table S1). (e) The balance between efficacy and side effects was evaluated agent by agent. (f) Although recommendations are primarily supported by the evidence reported in patients with primary SjS, the advice on topical and systemic management contained in these guidelines may be applicable to patients with associated (or secondary) SjS.

Systematic literature review

A previous systematic literature review (SLR) reported by the convenor in 2010[7] served to provide SC members with a background to initiate discussions and propose research questions for the SLR focused on the therapeutic management of SjS. On the basis of the research questions, PBZ and SR carried out the SLR between January 1986 and December 2017, with the supervision of the convenor and the methodologists. Summary-of-findings (SoF) tables were generated and levels of evidence (LoE) were determined according to the study design, using the Oxford CEBM standards[17] (online supplementary table S1). The SoFs of the SLR were presented to the SC, whose members formulated a first draft of recommendations based on this information, using electronic and cloud-based working strategies to review the literature search, making comments and maintaining open communication for electronic discussion and amendments. The SLR informing the SC and TF and a detailed description of the methods is published separately. [18] (

Task Force

The TF (online supplementary appendix 1) included 77 specialists in rheumatology, internal medicine, oral health, ophthalmology, gynaecology, dermatology and epidemiology, statisticians, general practitioners, nurses and patient representatives from 30 countries of the five continents (Argentina, Australia, Brazil, Canada, China, Denmark, Egypt, Finland, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Norway, Poland, Portugal, Slovenia, South Korea, Spain, Sweden, Switzerland, the Netherlands, Turkey, the UK and the USA). All TF members declared all potential conflicts of interest. After presentation of the SLR results and the SC proposals to the TF in the first face-to-face meeting, the TF was split into nine breakout working groups (see online supplementary text). Each group proposed draft language and diagnostic/therapeutic algorithms for the respective recommendations to the whole TF. Safety aspects were addressed in each breakout group. Formal economic analyses were not performed, but cost aspects were considered throughout the process. Representatives of each breakout group reported the results of the respective deliberations and presented proposals for the wording of individual recommendations to the whole TF for further discussion and refinement in the second face-to-face meeting.

Consensus findings

After the second meeting, a web-based Delphi procedure was carried out using online voting.[19] The Delphi procedure was designed by MR-C and PB-Z, and developed, managed and analysed by BK using Google Forms; all clinical experts in SjS included in the TF were invited to participate in the Delphi procedure. For an overarching principle or recommendation to be accepted for the final document, TF members were asked to grade for priority according to the level of importance in the daily therapeutic management of SjS (from 1 as unimportant, no priority, no relevance to 5 as very important, a most relevant point, first-order priority); a specific section allowed the inclusion of comments suggested to accompany individual items. Recommendations scoring ≥4 ('important') by >80% of participants were accepted; if this result was not achieved, the respective text was amended and subjected to a second electronic ballot. The approved recommendations were subjected to

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Table 1 Overarching (A–C) and specific (1–12) recommendations

	LoE	GoR	Vote (%)	LoA (0–10)
A.Patients with SjS should be managed at, or in close collaboration with, centres of expertise following a multidisciplinary approach	NA	NA	90	9.2
B.The first therapeutic approach for dryness should be symptomatic relief using topical therapies	NA	NA	93	8.9
C.Systemic therapies may be considered for the treatment of active systemic disease	NA	NA	90	9.1
1.Baseline evaluation of salivary gland function is recommended before starting treatment for oral dryness	5	D	81	8.7
2.The preferred first therapeutic approach for oral dryness according to salivary gland function may be:	1a/*1b	B	88	8.7
2.1. Non-pharmacological stimulation for mild dysfunction;				
2.2. Pharmacological stimulation* for moderate dysfunction;				
2.3. Saliva substitution for severe dysfunction				
3.The first-line therapeutic approach to ocular dryness includes the use of artificial tears and ocular gels/ointments	1a	B	98	9.5
4.Refractory/severe ocular dryness may be managed using topical immunosuppressive-containing drops* and autologous serum eye drops	1a/*1b	B/D	94	9.1
5.Concomitant diseases should be evaluated in patients presenting with fatigue/pain, whose severity should be scored using specific tools	5	D	93	9.0
6.Consider analgesics or other pain-modifying agents for musculoskeletal pain, considering the balance between potential benefits and side-effects	4	C	89	8.9
7.Treatment of systemic disease should be tailored to organ-specific severity using the ESSDAI definitions	4	C	89	9.0
8.Glucocorticoids should be used at the minimum dose and length of time necessary to control active systemic disease	4	C	85	9.6
9.Immunosuppressive agents should be mainly used as GC-sparing agents, with no evidence supporting the choice of one agent over another	4	C	82	8.9
10.B-cell targeted therapies may be considered in patients with severe, refractory systemic disease	1b	B	98	8.6
11.The systemic organ-specific therapeutic approach may follow, as a general rule, the sequential (or combined) use of GCs, immunosuppressive agents and biologics	5	D	98	8.6
12.Treatment of B-cell lymphoma should be individualised according to the specific histological subtype and disease stage	4	C	88	9.7

LoE and GoR according to the Oxford Centre for Evidence-based Medicine—LoE (March 2009). Vote (%): % of participants scoring the recommendation as at least 'important' (score of ≥4 on 5-point scale). LoA: mean score (scale of '0' as no agreement, '10' full agreement).
ESSDAI, EULAR Sjögren's syndrome disease activity index; EULAR, European League Against Rheumatism; GC, glucocorticoid; GoR, grade of recommendation; LoA, levels of agreement; LoE, levels of evidence; NA, not applicable.

an anonymous electronic vote on the levels of agreement (LoA). Each recommendation was adjudicated on a scale of 0–10 (0, no agreement; 10, full agreement).

The draft of the manuscript was written by MR-C and PB-Z and was sent to TF members for comment and, after incorporating these comments, to the EULAR Executive Committee for review and approval. Final remarks were obtained from members of the TF and the Executive Committee and addressed in the manuscript (all modifications required approval by the SC), which was then submitted with the final approval of the EULAR Executive Committee after being presented in the EULAR 2019 meeting.[20]

RESULTS

General recommendations

As in other EULAR recommendations, the TF endorsed the presentation of general principles for the management of patients with SjS as overarching, general consensus-based recommendations, since the contents were so generic that there was no requirement to base them on the SLR (table 1).

Patients with SjS should be managed at, or in close collaboration with, centres of expertise using a multidisciplinary approach(*LoE na; LoA 9.2*)

SjS may be a serious systemic disease, not only due to the heavy impact on the health-related quality of live (HRQoL) of the predominant symptoms (the triplet of dryness, fatigue and pain), but also due to the involvement of internal organs (systemic involvement) and the excess mortality caused by cancer (lymphoma). The low frequency of SjS in the general population, combined with a heterogeneous glandular/systemic clinical expression, makes it difficult to ensure a standardised depth of expertise in managing the disease in non-specialised clinical settings. Therefore, we recommend organising SjS management in and around centres of expertise, including professionals with solid clinical experience in assessing patients with SAD. Assessment of SjS patients requires expert guidance, not only to confirm the diagnosis by ruling out non-autoimmune aetiologies (especially for sicca symptoms), but also to evaluate the extent of organs damaged and to design a specific personalised follow-up according to the clinical and biological patient phenotype at diagnosis.[21] A multidisciplinary approach involving various health professionals is essential, with a central role for specialists in autoimmune diseases, who should act as the coordinator of diagnostic and therapeutic healthcare processes, based on a shared-decision policy between the patient and the specialist. The involvement of primary care physicians and other health professionals is highly recommended in the management of SjS patients.

The first therapeutic approach to dryness should be symptomatic relief using topical therapies (*LoE na; LoA 8.9*)

More than 95% of SjS patients present with sicca symptoms,[22] which have a significant impact on the HRQoL.[23–25] Studies that have evaluated the natural history of glandular function in primary SjS (summarised by Haldorsen *et al*)[26] report that, except in early stages of the disease, dysfunction may remain stable for long periods of time (up to 12 years) and have a chronic course, and no study has demonstrated that any therapeutic intervention can reverse glandular dysfunction and, therefore, can cure sicca symptoms. Since the complete disappearance of dryness, which is the desired target for all patients,

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Table 2 Glossary and definitions

Term	Definition	Examples
1.Nomenclature of therapies 1.1. Topical therapies 1.2. Systemic therapies	1.1. Interventions directly applied to the mucosal surfaces involved 1.2. Drugs administered orally or intravenously for systemic disease	1.1. Saliva substitutes, ocular tears 1.2. Antimalarials, glucocorticoids, immunosuppressive agents, intravenous immunoglobulins, biologics
2.Disease activity terms 2.1. Systemic disease 2.2. Active systemic disease 2.3. Severe systemic disease 2.4. Refractory systemic disease 2.5. Therapeutic response	2.1. Disease involvement that affects or has affected any of the organs/systems included in the clinESSDAI score 2.2. Patients with clinESSDAI score ≥1. 2.3. Patients with ESSDAI score >14, or high activity in any of the ESSDAI domains with a definition of high activity 2.4. Systemic manifestation/s refractory to SOC. 2.5. Decrease of ≥3 points in the global ESSDAI score	2.1. All ESSDAI domains except biological domain 2.2. Systemic activity is classified as low if ESSDAI is 1–4 (if not only due to biological domain), moderate between 5–13 and high ≥14. 2.3. Lymphadenopathy and lymphoma, articular, cutaneous, pulmonary, renal, muscular central and peripheral neurological and haematological domains. 2.4. Due to the diversity of systemic manifestations, SOC (first-line therapeutic approach) has been defined for each systemic manifestation (figure 3) –
3.Ocular dryness 3.1. Refractory 3.2. Severe	3.1. Refractory ocular dryness is defined as not improvement after using the best-available SOC and ruling out other SjS-unrelated processes, 3.2. Severity should be defined after a specific ophthalmological evaluation of corneal damage by ocular scores:	3.1. SOC defined as the maximum use of artificial tears and ointments according to the previous recommendation 3.2. Measurement of the OSS and OSDI ocular scores
4.Recommended instruments of measure 4.1. Salivary gland function 4.2. Corneal damage 4.3. Fatigue 4.4. Pain 4.5. Quality of life 4.6. Systemic disease	4.1. UWSF, SWSF 4.2. OSS, OSDI 4.3. ESSPRI domains, ProFAD 4.4. ESSPRI domains, BPI 4.5. ESSPRI 4.6. ESSDAI, clinESSDAI	
5.Potential life-threatening systemic manifestations	5.1. Cutaneous domain 5.2. Pulmonary domain 5.3. Renal domain 5.4. Muscular domain 5.5. Peripheral nerve system domain 5.6. CNS domain 5.7. Haematological domain	5.1. Diffuse vasculitis with ulcers 5.2. ILD with NHYA III/IV 5.3. Renal failure; rapidly-progressive glomerulonephritis; hypokalaemic paralysis 5.4. Muscular involvement with severe weakness 5.5. Neuropathy (including ganglionopathy and polyradiculopathies) with severe motor deficit/ataxia; cryoglobulinemic-related multineuritis 5.6. Demyelinating disease with motor deficit; cerebral vasculitis presenting with focal deficit; myelitis; meningoencephalitis 5.7. Severe haemolytic anaemia (<80 g/dL, <50 x109/L); severe autoimmune thrombocytopenia (<50 000/mm3)

BPI, brief pain inventory; CHB, congenital heart block; CIDP, chronic inflammatory demyelinating polyradiculopathy; CNS, central nervous system; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; EULAR, European League Against Rheumatism; G-CSF, granulocyte colony-stimulating factor; ILD, interstitial lung disease; KCS, keratoconjunctivitis sicca; LIP, lymphoid interstitial pneumonitis; MMF, mycophenolate mofetil; MP, methylpredisolone; MS, multiple sclerosis; NAC, N-acetylcysteine; NHYA, New York Heart Association; NMOSD, neuromyelitis optica spectrum disorder; NSIP, non-specific interstitial pneumonitis; OP, organising pneumonitis; OSDI, Ocular Surface Disease Index; OSS, Ocular Staining Score; PN, peripheral neuropathy; ROR, retinoic acid-related orphan receptor; RTX, rituximab; SjS, Sjögren syndrome; SOC, standard of care; STAT, signal transducer and activator of transcriptionm; SWSF, stimulated whole salivary flows; TOR, mammalian target of rapamycin; UIP, usual interstitial pneumonitis; UWSF, unstimulated whole salivary flows.

is at present unreachable, the TF recommends exploring the use of other, more realistic outcomes, such as the minimal clinically-important improvement or the patient-acceptable symptom state, following the corresponding ESSPRI definitions,[13] always closely aligned with patient education, including coping strategies. The chronic course of SjS means a daily, long-term use of therapies and, in this scenario, it is reasonable to recommend the use of therapies with a minimum of (or at least tolerable and reversible) side effects. This is overwhelmingly fulfilled by topical therapies (see definition in table 2). Various studies and Cochrane SLRs support the daily use of topical therapies for the symptomatic relief of dryness, with a significant improvement in HRQoL without significant side effects.[7 27 28] These therapies should be immediately initiated after objective confirmation of glandular dysfunction.

Systemic therapies may be considered for the treatment of active systemic disease (*LoE na; LoA 9.1*)

Systemic disease is a key prognostic determinant of SjS and is linked to autoimmune-mediated organ/s dysfunction that may eventually become irreversible. The use of systemic immunomodulatory/immunosuppressive therapies (glucocorticoids (GCs), antimalarials, immunosuppressive agents, intravenous immunoglobulins and biologics) should be restricted to patients with active systemic disease (see definition in table 2) but only after a careful organ-by-organ evaluation of both severity and organ damage, since not all patients with active systemic disease will necessarily require systemic therapy (this was why the original wording using 'should be' was changed to 'may be'). As a general rule, the management of systemic features in SjS should follow a schedule consisting of a two-stage sequential regimen as used in other SAD, including a first intensive immunosuppressive approach targeted to restore organ function (induction of remission) as soon as possible, followed by a second therapeutic course aimed at maintaining the initial therapeutic response (maintenance of remission). Unfortunately, there are no available data in patients with SjS to support specific recommendations on the need for/duration of induction and maintenance therapies, which should therefore be decided on case-by-case.

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Specific recommendations

The 12 specific recommendations form a logical sequence, starting with the management of the central triplet of symptoms (dryness, fatigue and pain) followed by the management of systemic, extraglandular disease (table 1).

Baseline evaluation of salivary gland function is recommended before starting treatment for oral dryness (*LoE 5, LoA 8.7*)

The therapeutic approach to oral dryness should be driven by the baseline measurement of salivary glandular function, and not by the patient's subjective feelings, since environmental and personal stressing factors may influence the subjective feeling of dryness,[29] which often does not match with the objective measurement of glandular function. We recommend the baseline evaluation of salivary glandular function by measuring whole salivary flows before starting therapeutic interventions, always ruling out SjS-unrelated conditions (ie, candidiasis, burning mouth syndrome); salivary scintigraphy may also be considered.[30] This item elicited significant discussions about the specific tests for measuring glandular function (unstimulated whole salivary flows and stimulated whole salivary flows (SWSF), and salivary scintigraphy), especially the use of SWSF and salivary scintigraphy, which were considered as complicated tests in daily practice by several TF members, and not always available in all clinical settings.

The preferred first therapeutic approach for oral dryness according to salivary gland function may be: Non-pharmacological stimulation for mild dysfunction; pharmacological stimulation for moderate dysfunction*; saliva substitution for severe dysfunction (*LoE 1a/*1b, LoA 8.7*)

On the basis of the results obtained in the measurement of salivary gland function, the therapeutic approach to oral dryness may be initiated based on two mechanisms: salivary gland stimulation (non-pharmacological or pharmacological) or saliva substitution (figure 1).[31]

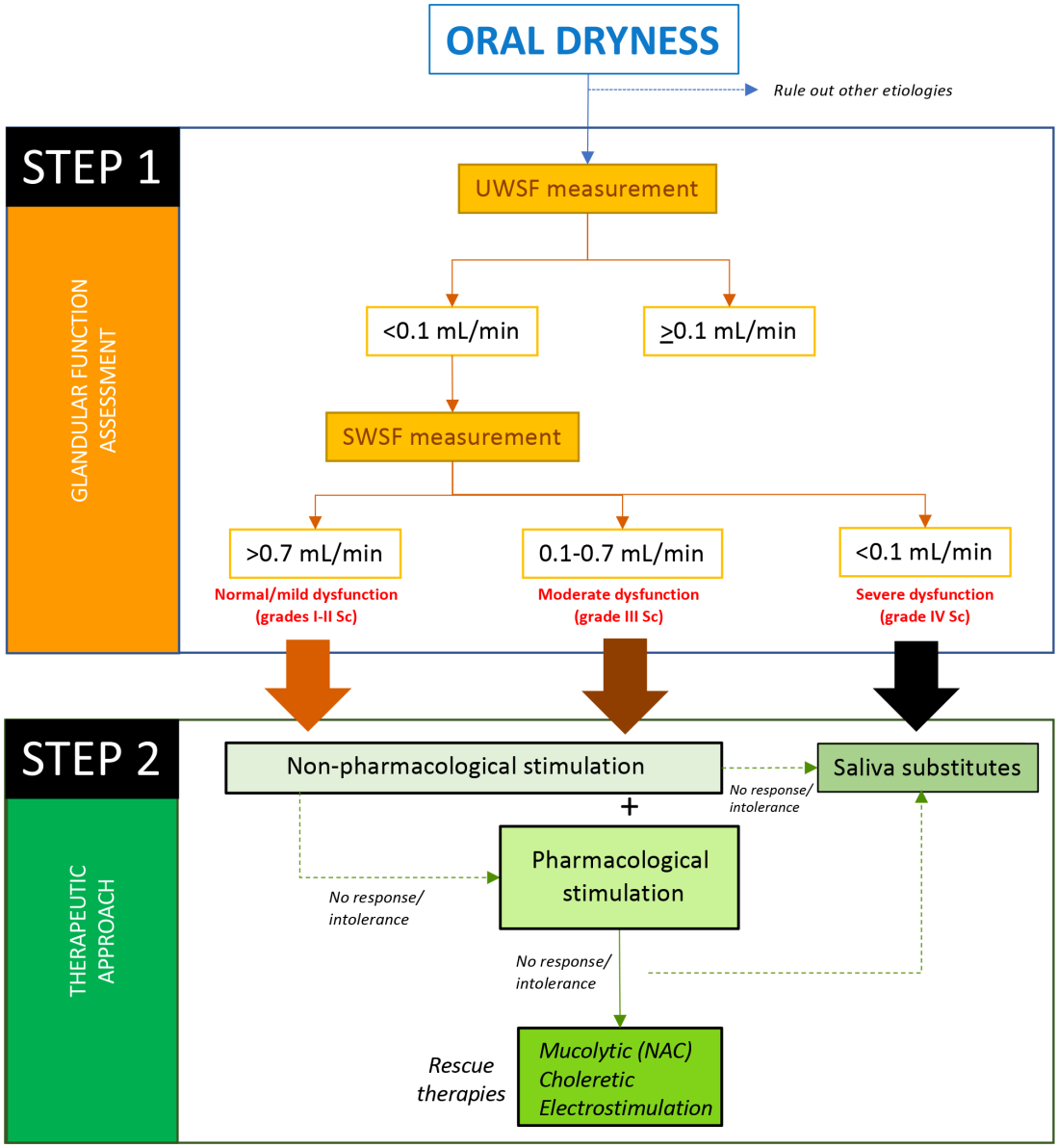

Figure 1 Algorithm of glandular function assessment and therapeutic approach in patients with primary SjS presenting with oral dryness. SjS, Sjögren syndrome; SWSF, stimulated whole salivary flows; UWSF, unstimulated whole salivary flows.

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Non-pharmacological stimulation

In patients with mild glandular dysfunction, we recommend non-pharmacological glandular stimulation as the preferred first-line therapeutic approach, using gustatory stimulants (sugar-free acidic candies, lozenges, xylitol) and/or mechanical stimulants (sugar-free chewing gum) since, in these patients, glandular function can be stimulated (figure 1). With no evidence available for pSjS-2002 patients, evidence was extrapolated from a Cochrane SLR[27] focussed on the therapeutic management of oral dryness; the authors concluded that all non-pharmacological interventions evaluated relieve subjective symptoms to some, unquantified degree, without strong evidence that any intervention was more effective than another, although no study evaluated the therapeutic response according to the degree of salivary gland dysfunction.[27]

Pharmacological stimulation

In patients with moderate glandular dysfunction, pharmacological stimulation with muscarinic agonists may be considered. Two drugs (pilocarpine and cevimeline) are licensed for the treatment of oral dryness, although only pilocarpine is licensed worldwide. The three pivotal randomised controlled trials (RCTs) included both primary and associated SjS patients fulfilling the 1993 criteria, and found significant improvements in visual analogue scale (VAS) dry mouth and salivary flow rates, with a high frequency of adverse events.[7] The available evidence in pSjS-2002 patients is limited to one small prospective study using pilocarpine that found improvement in subjective but not objective oral outcomes,[32] and a second study with no detailed information about overall efficacy and safety.[33] A third retrospective study which compares pilocarpine and cevimeline, only focussed on the safety profile,[34] and reported a better tolerance profile for cevimeline. The evidence is too limited to make a strong recommendation for pSjS-2002 patients (the best level of evidence should be extrapolated from RCTs including patients fulfilling the former 1993 criteria). For this reason, and together with the unfavourable safety profile of these drugs, we recommend offering a trial of muscarinic agonists to patients with moderate glandular dysfunction (or in those with mild dysfunction who are refractory or who do not wish to use non-pharmacological stimulation) (LoE 1b, GoR B) (figure 1). To reduce the main side effect (excess sweating), and based on clinical practice, some TF experts recommended increasing the dose progressively up to 15 to 20 mg/day when possible. In patients who are intolerant or non-responders to muscarinic agents, some choleretic (anetholtrithione) or mucolytic (bromhexine, N-acetylcysteine) agents used as secretagogues in SjS since the 1980s may be considered as rescue therapies due to their good safety profile in the absence of alternative therapeutic options, and taking into account the limitations of the study design and the marginal benefits reported by most studies.[7] According to the SLR results, for the treatment of oral dryness we do not recommend the use of hydroxychloroquine (no placebo-differences for subjective and objective oral outcomes in the pivotal RCT), oral GCs, immunosuppressive agents (overwhelmingly-negative results with excess side effects) or rituximab (no placebo-differences for subjective and objective oral outcomes in the two pivotal RCT and one meta-analysis)

Saliva substitution

Saliva substitution should be considered the preferred therapeutic approach to alleviate symptoms in patients with no residual glandular function (severe glandular dysfunction), in whom salivary glands cannot be stimulated, either by pharmacological or non-pharmacological interventions (figure 1). The ideal preparation will have a neutral pH and contain fluoride and other electrolytes, mimicking the composition of natural saliva; saliva substitutes are available commercially in the form of oral sprays, gels and rinses.[10] Only one prospective study evaluated pSjS-2002 patients[35] and found no statistically-significant placebo-differences for the primary outcome, although significant improvements were reported in some subjective oral outcomes, with no side effects reported. Evidence can be extrapolated from a Cochrane SLR that evaluated the effectiveness of topical treatments for any-cause dry mouth; the review found no superiority for any therapeutic option.[27] In spite of the limited evidence available, we recommend their use in the target population because, in the experience of TF members, patients often report increased oral comfort without significant side effects.[10] Oral gel-like formulations may be useful in patients with an acceptable salivary flow output, particularly when they complain about nocturnal oral dryness, although these patients often have a poor tolerance to saliva substitutes due to the sticky feeling caused by their application, which may be reduced by diluting the saliva substitute. Pretherapeutic evaluation of salivary function may also aid the choice of a specific formulation of saliva substitutes (gel, saliva substitute—diluted or not,mouth rinses), with less thick/dense preparations being preferred for patients with a better-preserved glandular function.[36] The preferred first-line use of saliva substitutes in patients with no salivary output elicited an intense debate within the TF, probably due to the apparent paradox of using a topical therapy in patients with severe glandular involvement. Several TF members expressed a dissenting view, stating that saliva substitutes should be used in all patients with oral dryness, irrespective of glandular function. Whether or not a saliva substitute is used, a neutral pH sodium fluoride gel should be prescribed to all patients with severe salivary dysfunction to prevent rampant caries.

The first-line therapeutic approach to ocular dryness includes artificial tears and ocular gels/ointments (*LoE 1a, LoA 9.5*)

The first line of therapy for ocular dryness should be volume replacement and lubrication using artificial tears (AT) and ocular gels, whose main ingredients are lubricants with a polymeric base or viscosity agent (methylcellulose, hyaluronate) with the aim of adding volume to the tear lake, increasing the time the AT remain on the ocular surface, and cushioning the ocular surface to reduce friction between lid and globe.[37] All SjS studies testing AT (only one in pSjS-2002 patients) found significant improvements for both subjective and objective ocular outcomes, while a recent Cochrane review on the use of AT for dry eye syndrome showed that they are safe and effective.[28] We recommend that all SjS patients presenting with ocular dryness and/or abnormal ocular tests should use AT containing methylcellulose or hyaluronate at least twice daily, with the frequency increased to as often as hourly, as indicated by symptoms and/or objective signs. The use of preservative-free formulations of AT is mainly recommended in patients requiring four or more applications per day. Ophthalmic ointments are thicker than AT and may be used to provide symptom control overnight; they are typically used before bedtime because they produce blurred vision and their use should be followed by morning lid hygiene to prevent blepharitis.[37]

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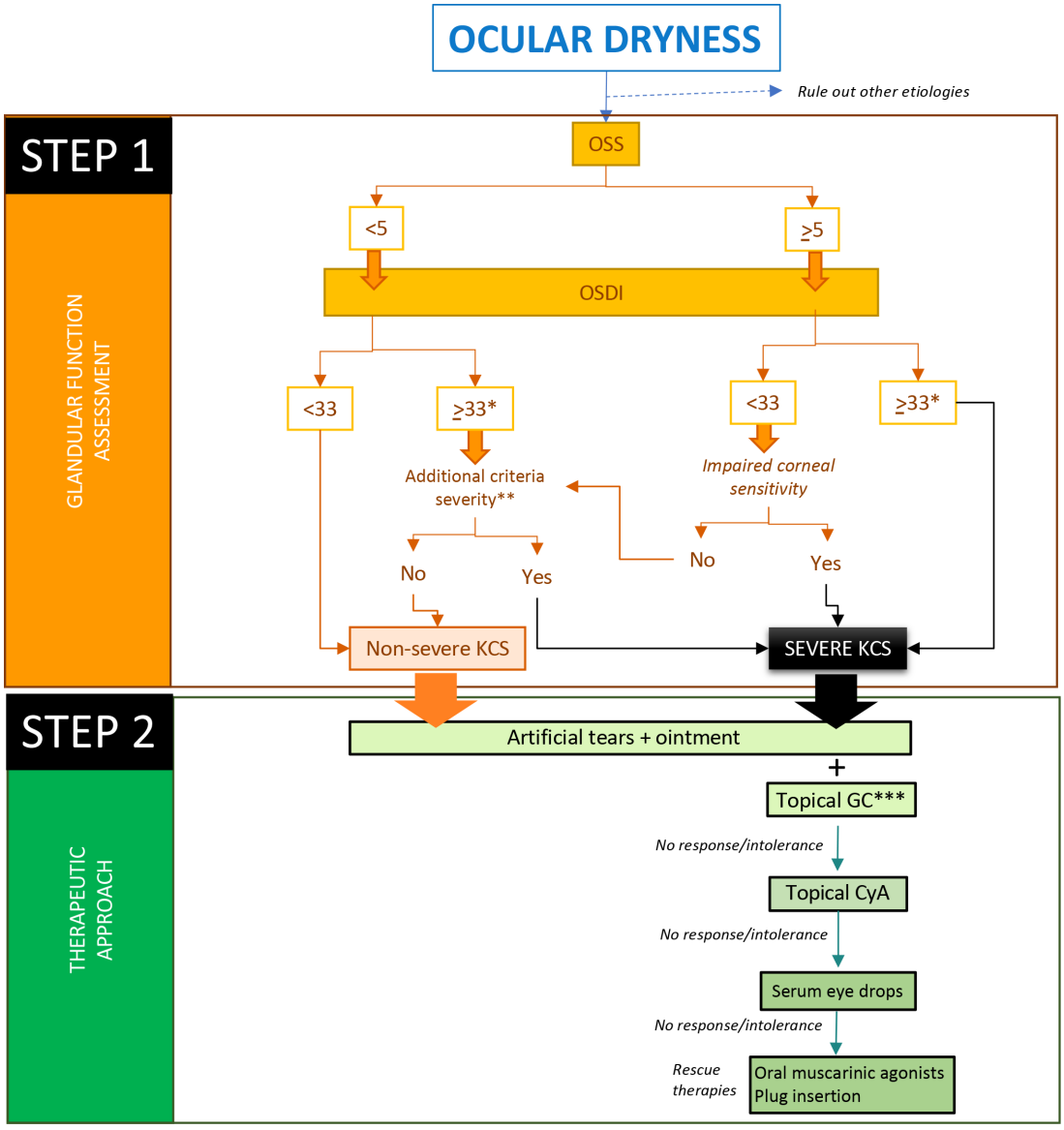

Figure 2 Algorithm of glandular function assessment and therapeutic approach in patients with primary SjS presenting with ocular dryness. *Consider neuropathic pain if OSS≤1. **Additional criteria for severity: (1) impaired visual function (photophobia, visual acuity modification or low contrast sensitivity); (2) blepharospasm (secondary to ocular inflammation); (3) severe meibomian gland disease or eyelid inflammation. ***For short-term indications (2–4 weeks). CyA, ciclosporin A; GC, glucocorticoid; OSS, ocular staining score (Whitcher[107] JP, *et al*. Am J Ophthalmol. 2010;149:405–15). OSDI, ocular surface disease index (adapted from Baudouin C,[108] *et al*. Br J Ophthalmol 2014;98:1168–1176); SjS, Sjögren syndrome.

Refractory/severe ocular dryness may be managed using topical immunosuppressive-containing drops* and serum eye drops (*LoE 1a/*1b, LoA 9.1*)

Patients with refractory or severe ocular dryness should be managed by an ophthalmologist with substantial experience in corneal disease wherever possible. Refractory ocular dryness is defined as patients who do not improve after using the best-available standard of care (SOC) (defined as the maximum use of AT and ointments according to the previous recommendation) after ruling out other SjS-unrelated ocular processes (ie, blepharitis), while severity should be defined according to the results obtained in a specific ophthalmological evaluation of corneal damage by measuring the OSS, together with patient symptoms as assessed by the Ocular Surface Disease Index (figure 2).

Topical NSAIDs/corticosteroids

Topical ocular non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids may be prescribed by ophthalmologists as a short-term therapeutic approach (maximum 2–4 weeks), as adverse events may occur with continued use of topical NSAIDs (corneal–scleral melts, perforation, ulceration and severe keratopathy) or topical corticosteroids (infections, increased intraocular pressure and worsening/development of cataracts).[37] Evidence in pSjS-2002 patients is limited to one small case-control study[38] using topical fluorometholone which found no significant differences in comparison with topical ocular ciclosporin A (CyA).

Topical CyA

In December 2002, an ophthalmic formulation containing 0.05% CyA was approved by the Food and Drug Administration to treat dry eye disease in the USA based on the results of two RCTs including patients with keratoconjunctivitis sicca (SjS patients were included in variable proportions).[7] There are no specific RCTs carried out in pSjS-2002,[39 40] and only one recent case-control study, which reported no significant differences

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between groups in comparison with topical fluorometholone, with a higher frequency of moderate-to-severe transient burning sensation in patients receiving CyA.[38] Ophthalmologists may consider the use of ocular CyA drops in patients with refractory or severe ocular dryness requiring repeated courses of glucocorticoid tear drops. The promising results of a recent small trial using tacrolimus tear drops[41] required further confirmation in large trials.

Serum tear drops

In SjS patients, the role of autologous or allogenic serum has been tested in small uncontrolled studies showing inconsistent benefits (no improvement in all objective ocular outcomes evaluated). A recent Cochrane SLR on the use of serum tear drops for dry eye syndrome[42] has confirmed inconsistencies in their possible benefits both for symptoms and objective measures, with no evidence of an effect after 2 weeks of treatment. Only one study has been carried out in pSjS-2002 patients, which showed significant improvement in some ocular outcomes.[43] The difficulties in preparation, the need to refrigerate the drops, and the potential risk of contamination should be taken into account.[37 44] The TF recommended that serum tear drops may be considered in patients who are non-responders or intolerant to topical CyA tear drops.

Rescue therapies

Other therapeutic interventions may be considered after failure of the above-mentioned therapies, including topical and systemic therapies. A recent Cochrane SLR reviewing the use of plugs for dry eye syndrome[45] found that the evidence was very limited, and concluded that improvements in subjective and objective ocular outcomes were inconclusive. Two studies have been carried out in primary-2002 SjS patients: the first found no significant differences between groups (insertion of plugs vs AT),[46] and the second reported improvement in only two of four ocular outcomes evaluated.[47] With respect to systemic therapies, oral muscarinic agonists may be considered on the basis of the improvement of subjective (not objective) ocular outcomes.[7] According to the SLR results, for the treatment of ocular dryness we do not recommend the use of hydroxychloroquine (no placebo-differences for subjective and objective ocular outcomes in the pivotal RCT), immunosuppressive agents (overwhelmingly negative results with excess side effects) or rituximab (no placebo-differences for subjective and objective oral outcomes in the two pivotal RCT and one meta-analysis).

In summary, although patients with refractory/severe ocular dryness may require a more intensive ophthalmological follow-up and, probably, more complex therapies, including immunosuppressive-based tear drops (topical corticosteroids or CyA) and serum tear drops, the low level of current evidence for the use of these complex ophthalmological therapies in primary SjS-2002 patients do not permit the TF to establish a strong preference among the options. The expertise of the ophthalmologist and the specific characteristics of the patient will drive both the preferred first-line therapy and the sequential use of the therapeutic interventions.

Concomitant diseases should be evaluated in patients presenting with fatigue/pain, whose severity should be scored using specific tools (*LoE 5, LoA 9.0*)

Patients with primary SjS often present with general symptoms, of which most frequent are non-inflammatory joint/muscle pain and fatigue/weakness, which may have a much greater impact on the HRQoL than sicca features, as reported in cross-sectional studies.[23–25] Unfortunately, these symptoms are very unspecific and could be related to a wide range of concomitant pathologies (osteoarthritis, hypothyroidism, hypocortisolism, vitamin deficiencies, depression, neoplasia) and even to some systemic complications of systemic SjS (arthritis, anaemia, hypokalaemia, osteomalacia, lymphoma, small-fibre neuropathy). A specific comment is needed on the association between SjS and some somatic functional syndromes such as chronic fatigue syndrome and fibromyalgia, whose peak of incidence occurs in the same population subset as SjS (middle-aged women).[21] No studies have confirmed a solid aetiopathogenic autoimmune link between SjS and chronic fatigue syndrome/fibromyalgia[48] beyond the evident epidemiological overlap. Since the association of these somatic syndromes could heavily influence both the patient and physician global health status evaluation, we recommend searching for these syndromes using standardised recommendations,[49] and measuring the severity of pain and fatigue using specific scales such as the corresponding ESSPRI domains, the Profile of Fatigue (for measuring fatigue) and the Brief Pain Inventory (for measuring pain).[50] SjS patients may describe various kinds of pain and fatigue, and the use of both general and SjS-specific questionnaires will permit not only a standardised measurement of their potential impact on HRQoL, but consideration of their influence when specific therapeutic interventions are initiated.[10 51]

Consider analgesics or other pain-modifying agents for musculoskeletal pain, taking into account the balance between potential benefits and side-effects (*LoE 4, LoA 8.9*)

With respect to SjS-related musculoskeletal pain, a clear pretherapeutic differentiation must be made clinically between joint pain (arthralgia) and joint inflammation (arthritis, tenosynovitis).[52] The ESSDAI score classifies arthralgia in the hands, wrists, ankles and feet accompanied by morning stiffness (>30 min) as low articular activity level, always ruling out concomitant osteoarthritis. Arthritis is clinically diagnosed on the basis of objective inflammation of ≥1 joints (heat, redness and swelling in the physical examination of the affected joint) supported by ultrasound studies when in doubt, and the ESSDAI score classifies the severity of arthritis according to the number of joints involved (moderate ≤5 joints, high >5).[12] The therapeutic management of arthritis is included in the systemic recommendations. (a) In patients presenting with acute musculoskeletal pain, consider acetaminophen or NSAIDs for symptomatic relief, always for less than 7–10 consecutive days at full dosage and considering the side effects and underlying comorbid diseases. In real life, a large retrospective study in 188 primary 2002 SjS patients with joint involvement reported that nearly one third had a rapid clinical response to the short-term use of analgesics/NSAIDs.[53] Topical formulations of NSAIDs (topical diclofenac or ketoprofen) may be effective for local pain with fewer side effects,[54] but there is no available evidence in SjS patients.[55] (b) In patients with frequent episodes of acute musculoskeletal pain, the use of hydroxychloroquine has been proposed based on its comparable use in other SAD such as systemic lupus erythematosus (SLE). Although uncontrolled studies have reported improvement in joint pain, the pivotal RCT failed to demonstrate that hydroxychloroquine improved pain after 24 weeks of treatment in comparison with placebo, although a statistical trend was reported (p values between 0.06 and 0.10) at 12, 24 and 48 weeks).[56] Taking this positive trend, the lack of reported cases of retinal toxicity or severe adverse events, and the lack of pharmaceutical

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alternatives with a similar indication/safety profile, the TF members agreed to consider the use of hydroxychloroquine in some patients with frequent episodes of articular pain. In real life, the study by Fauchais *et al*[53] reported the use of hydroxychloroquine in more than half the patients presenting with joint involvement. With respect to the use of biological agents to treat these symptoms, the data from the two pivotal RCTs[57 58] on the effect of rituximab on pain and fatigue reported no significant differences in comparison with placebo for both pain and fatigue VAS (although some differences were found at intermediate evaluation points in the French study), together with no significant placebo-differences in quality-adjusted life-year but with a fivefold greater economic cost,[58] while a recent meta-analysis[59] confirmed no significant differences after combining the results of these trials. In addition, a small RCT using anakinra found no significant reduction in fatigue in its primary endpoint,[60] while the promising results obtained in two small open-label studies (<30 patients) using epratuzumab[61] or abatacept[62] must be confirmed in further large RCTs. Therefore, we consider that the off-label use of biological agents to treat only musculoskeletal pain (even as rescue therapy) is not currently warranted. (c) In patients with chronic, daily non-inflammatory pain, the management must be completely different, avoiding the repeated use of NSAIDs or GCs. The non-pharmacological management of pain should be emphasised, instead of going straight to prescribing medications for the symptoms. Therefore, the first therapeutic step should be to follow the same recommendations as those proposed for general chronic pain, by suggesting that physical activity and aerobic exercise are interventions with few adverse events that may reduce pain severity and improve physical function.[63] In addition, a small case-control study in primary SjS patients showed significant improvement in aerobic capacity, fatigue and ratings of perceived exertion and depression in patients allocated to the exercise group.[64] Antidepressants and anticonvulsants may be considered for chronic musculoskeletal pain, while patients with chronic neuropathic pain may require the use of gabapentin, pregabalin or amitriptyline (paying attention to potential exacerbations of dryness symptoms). Recent epidemiological data confirm that opioids must not be used.[65]

Treatment of systemic disease should be tailored to organ-specific severity using the ESSDAI definitions (*LoE 4, LoA 9.0*)

In non-specialised medical settings, primary SjS is often considered a chronic, non-life-threatening disease that only causes dryness, fatigue and pain. However, systemic involvement has been increasingly recognised as a key part of the disease, with a significant weight in dictating the prognosis and survival in retrospective studies.[66–69] The development of the ESSDAI by the EULAR-SS Task Force Group has provided a helpful, objective instrument to measure systemic involvement in primary SjS that is accepted worldwide. According to overarching principle C, we recommend that the use of systemic therapies (GCs, antimalarials, immunosuppressive agents, intravenous immunoglobulins, biologics) should be restricted to patients with active systemic disease (see definitions in table 2). However, the management of systemic features must be tailored to the specific organ involved and the severity evaluated by the ESSDAI.[69] As an overall rule, systemic therapies may be considered for most patients presenting with at least moderate activity in one clinical domain, or with a global moderate disease activity score (score ≥5). With respect to the definition of the therapeutic response in systemic SjS, the TF recommends using a reduction of ≥3 points in the global ESSDAI score.[70] It should also be considered that some systemic manifestations are not captured by the ESSDAI, including Ro-associated congenital heart block, Raynaud phenomenon, primary pulmonary hypertension, pleuritis, pericarditis, dysautonomia, interstitial cystitis and sensorineuronal hearing loss; these features require specific patient-by-patient management.

GCs should be used at the minimum dose and length of time necessary to control active systemic disease (*LoE 4, LoA 9.6*)

The frequent use of GCs in clinical practice in primary SjS patients[69 71 72] is not supported by reliable scientific evidence, since no controlled study has specifically evaluated their use for systemic disease. Available data come mainly from retrospective studies (online supplementary table S2) and case series/reports, which also highlighted the high rate of GC-related adverse events. We recommend that GCs should be used at the minimum dose and length of time necessary to control active systemic disease, administering pulses of methylprednisolone followed by doses of 0.5 mg/kg/d or lower as induction therapy in severe presentations (table 2), and doses<0.5 mg/kg/d in moderate/less-severe presentations, with a final target of withdrawing GCs in inactive patients as soon as possible or at least trying to target a maintenance dose of 5 mg/daily or less with the aid of GC-sparing immunosuppressive agents (see recommendation 'Synthetic immunosuppressive agents should mainly be used as GC-sparing agents, with no evidence supporting the choice of one agent over another (*LoE 4, LoA 8.9*)'). No available data in SjS patients support specific recommendations on the rate of de-escalation of the GC dose, or when a GC-sparing agent should be added, or the length of GC therapy, although we recommend tapering GCs as rapidly as clinically feasible. We recommend to follow the EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases.[73]

Synthetic immunosuppressive agents should mainly be used as GC-sparing agents, with no evidence supporting the choice of one agent over another (*LoE 4, LoA 8.9*)

Based on the potential development of chronic damage in patients with uncontrolled systemic disease, some patients may require long-term therapy with GCs, especially those with severe organ impairments.[69 71 72] In these patients, the addition of immunosuppressive agents as GC-sparing agents is justified, always weighing the potential benefits and risks. The use of immunosuppressive agents in primary SjS is based on the same level of evidence as that of GCs, since all reported studies (prospective uncontrolled studies, all including less than 50 patients) were principally centred on the efficacy in sicca features and laboratory parameters, but not on the efficacy in systemic disease, with an unacceptable rate of adverse events (ranging between 41% and 100%).[7] The lack of head-to-head studies comparing the efficacy and safety profile of immunosuppressive agents in primary SjS-2002 (leflunomide, methotrexate, azathioprine, mycophenolate, cyclophosphamide) does not permit a recommendation on the use of one agent over another, except when patient characteristics or comorbidities are considered with respect to the safety profile. In addition, there is no information available about the dose, route of administration and length of treatment and we recommend a case-by-case evaluation following similar rules to those reported for other SAD. Although some TF members suggested the use of monotherapy with immunosuppressive agents, there was no final consensus on this option due to the lack of studies demonstrating the efficacy

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of GC-free regimens in SjS, and the fact that more than 95% of reported cases using immunosuppressive agents in primary SjS-2002 received associated GCs (online supplementary table S2). Several immunomodulatory agents have been tested in SS, with marginal benefits or with an unacceptable rate of adverse events and are not recommended.[7]

B-cell targeted therapies may be considered in patients with severe, refractory systemic disease (*LoE 1b, LoA 8.6*)

The emergence of biological therapies in this century has increased the therapeutic armamentarium available for treating severe SjS. These new drugs have the highest level of evidence among all the drugs tested for SjS, not only because have they have been tested in a large number of patients (>1000), but also because most of reported RCTs in primary SjS have tested biologics. Unfortunately, their use in clinical practice is clearly limited by the lack of licensing. B-cell targeted therapies are the most frequently tested biological drugs, and include epratuzumab[61] and belimumab,[74 75] although the most widely studied B-cell target therapy is rituximab.[57 58 76–86]

Studies with available data on the efficacy of rituximab on systemic involvement have included more than 400 patients with primary SjS-2002 (online supplementary table S3), with a predominant use of the regimen of 2 doses of 1 g each administered 15 days apart.[7] Four main systemic outcomes were evaluated at different follow-up times in these studies: the global therapeutic response, organ-specific response, change in the global ESSDAI score and reduction in prednisone use. Uncontrolled studies have reported a global response rate of 60%–100% for systemic features, especially cryoglobulinemic features.[76 77 79 80 86] One small RCT[86] reported a significant reduction in reported extraglandular manifestations and improvement of musculoskeletal features at weeks 12 and 36 (p=0.029) and vasculitis at week 24 (p=0.03). Four studies (two retrospective, one case-control and one prospective) have reported a statistically-significant reduction in the global baseline ESSDAI score (from 9 to 20.3 to 2.5–5.2 after treatment).[77–80 84] In the two pivotal RCTs, Devauchelle *et al* found no differences in the mean ESSDAI improvement,[57] while Bowman *et al*[58] reported statistically-significant placebo differences at week 36 (p=0.03) and a statistically-significant trend at week 48 (p=0.07) in the log-transformed ESSDAI score. Three retrospective studies have demonstrated a statistically significant reduction in the daily dose of GCs.[76 79 80] In summary, the great majority of studies showed efficacy in at least one of the systemic outcomes analysed (global response, organ-specific response, ESSDAI reduction, prednisone reduction).

The results of the Efficacy and Safety of Belimumab in Subjects with Primary Sjögren's Syndrome open label trial[74] in 30 pSjS-2002 patients treated with belimumab showed a reduction in the mean ESSDAI score from 8.7 to 5.7 at week 28 (p<0.0001), with a decrease of at least 4 points in 40% of cases and improvements in

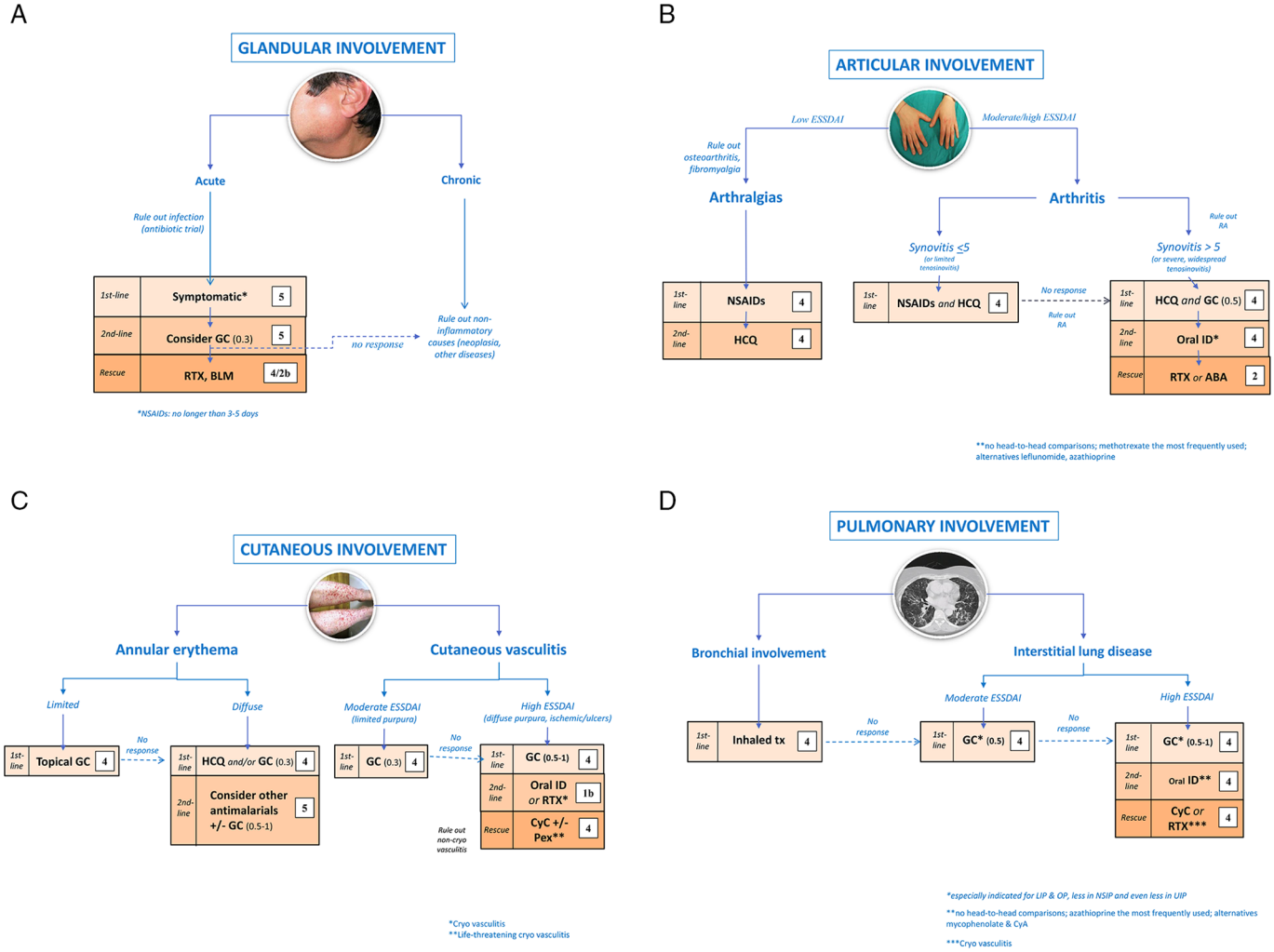

Figure 3 *(Continued)*

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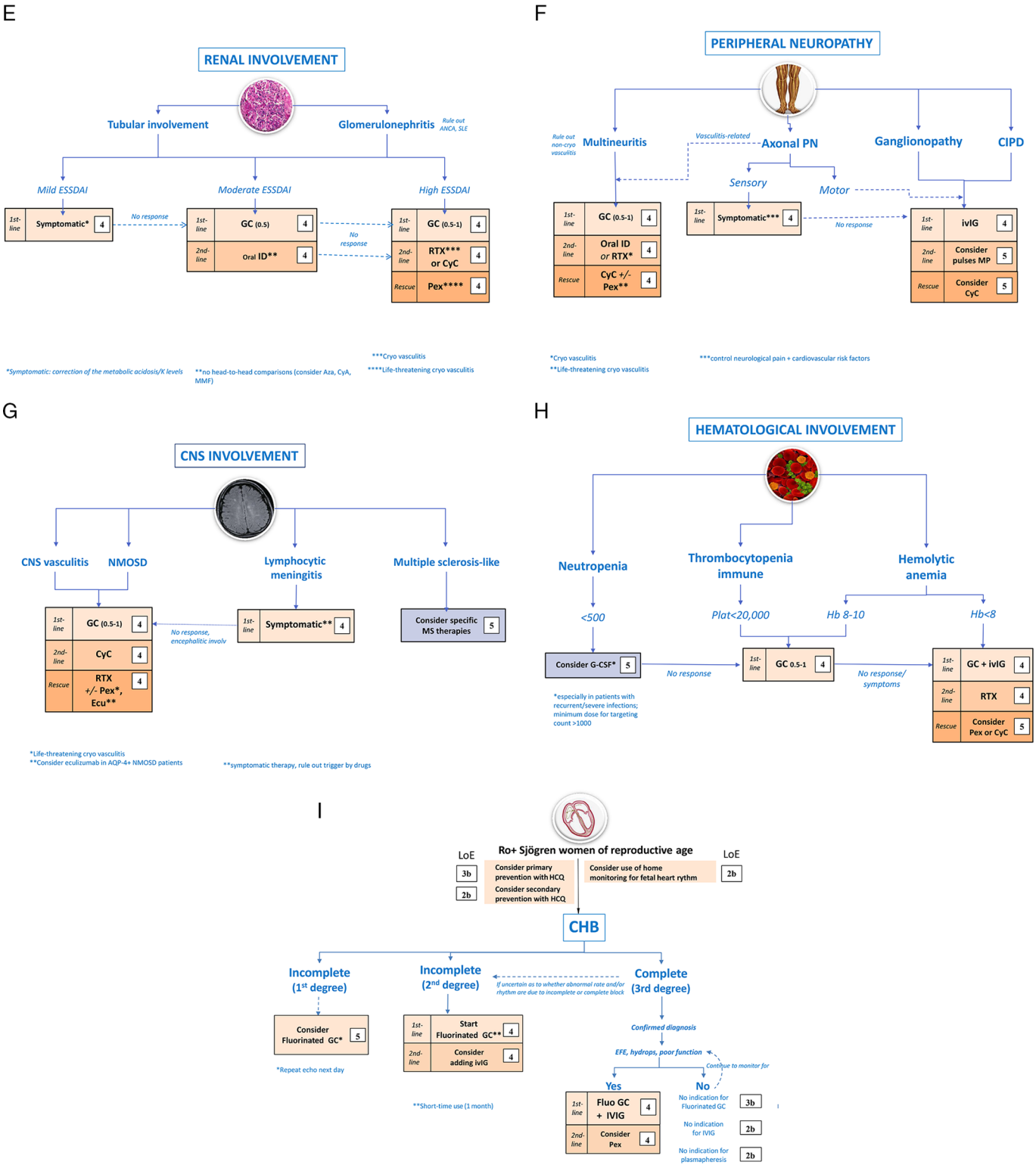

Figure 3 (A to I) Algorithm for the therapeutic approach to patients with primary SjS presenting with organ-specific systemic involvements. NSAIDs: no longer than 7–10 days. HCQ: hydroxychloroquine 200 mg/day. GC (recommended dose in mg/kg/day); short-term course whenever possible; consider methylprednisolone pulses in severe cases. ID: immunosuppressive agents, no head-to-head comparisons. CyC: cyclophosphamide pulses 0.5 g/15 day (maximum six pulses). Rituximab: rituximab 1 g/15 days (x2). BLM: belimumab; 10 mg/kg (0, 2 and 4 weeks and then every 4 weeks). ABA: abatacept 0, 2, 4 weeks and every 4 weeks. IVIg: intravenous immunoglobulins 0.4–2 g/kg 5 days. PEX: plasma exchanges. CyA, ciclosporin A; EULAR, European League Against Rheumatism; ESSDAI, EULAR Sjögren's syndrome disease activity index; GC, glucocorticoid; LoE, levels of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SjS, Sjögren syndrome.

parotid swelling in 77% of cases; of five patients previously refractory to rituximab, belimumab was effective in 3 (60%). In a study extension of the 19 patients that completed 1 year of treatment, a significant improvement was maintained.[75] With respect to the safety profile, one severe adverse event was reported (pneumococcal meningitis) after 6 infusions of belimumab.

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After intense discussion among the TF members and balancing the positive results of uncontrolled studies, the weak evidence reported by RCTs, and the fact that the trials were not primarily designed to evaluate the systemic response, we agreed that the use of rituximab may be considered (we changed the original wording of 'should be') in patients with severe, refractory systemic disease, and that the best indication is probably for symptoms linked to cryoglobulinemic-associated vasculitis,[87] with the possible use of belimumab as rescue therapy.

The systemic organ-specific therapeutic approach may, as a general rule, follow the sequential (or combined) use of GCs, immunosuppressive agents and biologics (*LoE 5, LoA 8.6*)

The recommended general sequential use of the three main categories of immunosuppressive agents in SjS is based on a similar approach to that reported for other SAD such as SLE or vasculitis, with no controlled studies supporting this approach in SjS. As a general rule, for most systemic involvements GCs (see recommendation 'GCs should be used at the minimum dose and length of time necessary to control active systemic disease *(LoE4, LoA9.6)*') may be considered the first-line option in patients with active systemic disease, and immunosuppressive agents and biologics as second/third line options to be used in patients intolerant or refractory to GCs, those with severe disease or those in whom long-term GC use is anticipated. In spite of the greater amount of scientific evidence data available for rituximab in comparison with GCs and immunosuppressive agents, the lack of licensing, the lack of controlled studies for systemic disease and the lack of head-to-head comparisons between rituximab and classic immunosuppressants (especially with respect to the safety profile) were issues to be considered. After an intense discussion among the TF members, the TF agreed to merge the two options as second-line therapies (adding a specific note about the use of rituximab as especially recommended for associated cryoglobulinemic vasculitis), always with a careful case-by-case assessment of the use of rituximab in an off-label context, evaluating potential benefits and adverse effects patient-by-patient (table 2), and taking into account the fact that their use will depend on drug availability and national regulations.

Unfortunately, after analysing the available evidence, no controlled data was identified to support a differentiated organ-guided therapeutic approach for systemic SjS, and some TF members recommend no strictly adherence to sequential therapy management, with an individualised therapeutic approach being preferable. However, on the basis of the results, principally from retrospective studies (online supplementary table S2), together with the clinical experience of the TF members, a list of consensus-based algorithms defining SOC and second/third line therapies was proposed for each clinical ESSDAI domain (figure 3A–I); Ro-associated congenital heart block (not included in the ESSDAI) was also included due to its prognostic significance. There was no consensus on the proposal to make recommendations for organ-specific maintenance therapeutic regimens.

Treatment of B-cell lymphoma should be individualised according to the specific histological subtype and disease stage (*LoE 4, LoA 9.7*)

Among the systemic manifestations of SjS, lymphoma is one of the worst complications, with standardised incidence ratios for B-cell lymphoma ranging between 7 and 9 in population-based studies and between 16 and 48 in hospital-based studies.[88] Although the vast majority of cells infiltrating the salivary glands of patients with primary SjS are T cells, the majority of lymphomas reported are of B-cell origin with a ratio between B and T-cell lymphomas of 15:1; three subtypes of B-cell lymphoma account for more than 90% of reported cases in primary SjS: mucosa-associated lymphoid tissue (MALT) lymphoma, other marginal zone lymphomas (MZL) and Diffuse large B cell lymphoma.[88] Following the diagnosis of lymphoma, therapy should be individualised according to the specific histological subtype defined according to the WHO 2016 classification[89] and the corresponding current therapeutic guidelines, with a personalised therapeutic approach driven by the haematologist/oncologist. For primary SjS-2002 patients diagnosed with low grade haematological neoplasia, some clinicians recommend a watchful waiting approach when lymphoma only affects the exocrine glands,[90] especially in the absence of constitutional symptoms, systemic features or B-cell activation biomarkers.[3] The decision to treat low-grade lymphomas or not must be discussed in a multidisciplinary committee, taking into account the fact that they are linked to the disease activity and are the ultimate stage of autoimmune B-cell activation. Moreover, low grade B-cell lymphomas have a potential risk of progression to more aggressive types of lymphoma.[3] In patients with disseminated MALT lymphoma or with concomitant high disease activity, chemotherapy may be considered on a case-by-case basis.[3] For patients with marginal zone lymphomas, small lymphocytic lymphoma (SLL) and lymphoplasmacytic lymphoma (LPL) in early disease stages (in particular, stage I or non-bulky stage II), treatment may include radiotherapy (with or without chemotherapy), although a watch-and-wait strategy could be an alternative to spare the side effects of therapy.[91] For patients with moderate/high grade haematological neoplasia, treatment is based on standard rituximab-based chemotherapy regimens. The benefit of adding rituximab to chemotherapy has been demonstrated in a meta-analysis in patients with follicular lymphomas, mantle cell lymphomas and other indolent lymphomas.[91] Rituximab plus fludarabine or bendamustine (BR) are the recommended first-line therapy for MZL, SLL and LPL; a recent study in 13 patients with pSjS-2002 (77% stage IV) complicated by MZL has reported the efficacy of the BR combination in all 13 cases, with improvement in the other SjS non-lymphomatous manifestations and with a good safety profile.[92]

DISCUSSION

The EULAR recommendations for the management of SjS with topical and systemic therapies management have been developed by a large, multidisciplinary, multiprofessional team. In summary, nine RCTs (only three including 120–130 patients), 18 prospective (all including between 10 and 50 patients) and five case-control studies were selected to support the scientific evidence presented here. This is a small number of studies that is not comparable with rheumatoid arthritis (RA) or with other, more closely-related diseases, such as SLE or systemic vasculitis. Therefore, the evidence accumulated in this century reveals SjS as a true orphan disease from a therapeutic point of view,[59 93] with the absence of any efficacious agent, a situation that is in clear contrast with the significant advances achieved in both basic and clinical research during this period. As a consequence of the limited evidence available, therapeutic decisions in daily practice are often based on a mix of reported expert opinions and personal experience, which may vary widely between countries: therefore, the present recommendations are based on the input of experts from 16 European countries and wide international representation from the other continents. In addition, SjS presents with a wide range of signs and symptoms (not only the key features of dryness, fatigue and pain, but also those derived from organ-specific systemic involvements and lymphoma), with

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a large number of different specialties involved and, therefore, with a wide variety of potential interventions. Methodologically, we have also taken into account the continuous changes in classification criteria since 1986 and, in consequence, the continuous changes in the target population classified as primary SjS. For this reason, we decided, in the Population, Intervention, Comparison, Outcomes and Study design strategy, to focus on the evidence collected from therapeutic studies including pSjS-2002 patients, since these criteria have been used for a longer and more-recent period and because of their similarity with the recent 2016 American College of Rheumatology (ACR)/EULAR criteria.[16]

In SjS, we are very far from the 'disease modification' concept as the mainstay of treatment (as used in other diseases such as RA, a concept that allows the use of the term disease modifying antirheumatic drugs for many drugs that have demonstrated the ability to prevent structural damage progression in RA). A rapid overview of the LoE that support each statement (table 1) shows that all recommendations for managing oral and ocular dryness are principally supported by evidence extrapolated from Cochrane SLRs that evaluated their management in mixed aetiological populations; on the management/prevention of dryness-related complications (oral ulcers, candidiasis, caries/dental complications, ocular infections), the management of dryness other than oral or ocular, or the role of non-therapeutic interventions in dryness, there was a very limited number of studies carried out in 2002 primary SjS patients, and we recommend following published guidelines.[9–11 37 94] With respect to the most frequently used synthetic drugs (GCs and immunosuppressive agents), the available evidence came from isolated uncontrolled studies. The only exceptions were for hydroxychloroquine and rituximab, which were both tested in well-designed RCTs, although there were no statistically-significant differences with respect to placebo for the primary outcome (efficacy in dryness, fatigue and pain). With respect to systemic disease, the use of rituximab was supported by a large number of studies, mainly uncontrolled. We are also very far from defining specific treatment targets (especially searching for remission in non-systemic features), but it may be useful to use the EULAR disease activity states,[70] considering that any higher disease activity has to be regarded as inadequate disease control, thus mandating a therapeutic intervention, or that low disease activity achieved after therapy may be potentially acceptable for some organs. In any case, as stated in previous EULAR recommendations,[95] communication with the patient to clarify and agree on the treatment goal and the means to attain it is of utmost importance. Monitoring should be frequent in patients with systemic active disease, although the frequencies of follow-up examinations should be adjusted in accordance with the individual disease activity state,[70] namely, more frequently, such as monthly, when patients have high disease activity, and less frequently, such as every 6–12 months, when patients have low disease activity.

Lessons should be learnt from the first biological tested in primary SjS (infliximab). The excellent results of tumour necrosis factor-targeted therapies in RA led to their testing in patients with primary SjS, in spite of the large pathological and clinical differences between the two diseases. After the report of promising results in small open-label studies (one of which has been recently retracted by the authors), the first well-designed RCT showed no differences between the infliximab and placebo arms for the primary outcome. The same disappointing results have been obtained for other drugs reported as efficacious according to uncontrolled data (hydroxychloroquine and rituximab) without significant results for the primary outcomes when tested in RCTs. In SjS trials, two common issues may help to explain the negative results. The first is the choice of primary end-points. Most studies used composite primary outcomes based mainly on the subjective evaluation of dryness, fatigue, pain[96] ; the strong influence of personal and environmental factors on the intensity of this triad of symptoms could explain the lack of significant differences (a higher rate of placebo-related response), together with inadequate patient selection (too low degree of disease activity), the influence of concomitant drugs and the heterogeneity of diagnostic tests. The composite ESSDAI to measure systemic activity was used in the most recent RCT as a secondary end-point and frequently calculated retrospectively (although one of the weaknesses of this outcome could be the difficulty in differentiating activity due to chronic damage in different domains). The preliminary results of two new RCTs where ESSDAI was the primary end-point demonstrated efficacy of the active drug versus placebo (anti-CD40 and the combination of leflunomide and hydroxychloroquine).[97 98] The second issue is the limited number of patients randomised (no more than 50–60 patients per arm), taking into account the clinical and immunological heterogeneity of SjS as an SAD (such as SLE or systemic vasculitis); in SLE, the pivotal trials that allowed the licensing of belimumab were obtained from two trials including nearly 1000 patients each. Some promising results recently reported in small open-label studies testing biologics (belimumab, anakinra) must be confirmed in further large well-designed RCTs, while advance results of a large trial in primary SjS do not indicate a clinical benefit of abatacept.[99] The current therapeutic pipeline in SjS, as shown by the *clinicaltrials.gov* webpage, is that the biologic therapeutic approach overwhelmingly used in SjS until now (targeting B-cell depletion) is shifting towards the evaluation of biologics targeting cytokines, T-cells and intracellular signalling pathways.[100] With respect to ongoing trials, considerable interest is centred on the B cell survival factor (BAFF) pathway, investigating the effect of monoclonal antibodies targeting BAFF-receptor or the association between B-cell depletion and BAFF inhibition. In addition, studies are testing inhibition of other pathways activating B cells. Lastly, four ongoing trials are testing other pathways or the use of other cytokine-based therapies including tocilizumab, abatacept, filgotinib (a janus kinase inhibitor) and human recombinant Il-2.

Therapeutic research in SjS should probably be reconsidered in order to explore new pathogenic targets outside the glandular tissue (ie, neuroendocrine pathways), and to search for a more personalised therapeutic approach based on genetic, clinical, immunological and/or histopathological characteristics. It is not improbable that future RCTs would benefit from more selected patient cohorts, possibly including newly diagnosed SjS patients, the findings of early salivary gland ultrasound changes,[101–103] or evidence of early high disease activity at diagnosis[22] before permanent damage has been established and the changes are still reversible. Patients with sicca-limited disease differ from those with systemic disease, as do immune-negative patients from those carrying Ro autoantibodies or cryoglobulins, while recent etiopathogenic studies are beginning to divide SjS patients according to the genetic profile between those with or without a predominant IFN-I gene expression signature.[104–106] Sensitivity analyses searching for a differentiated response to therapies in these subsets of patients (sicca-limited vs systemic; Ro+ vs Ro-; positive vs negative salivary gland biopsy; positive vs negative IFN-I signature) might help to better delineate the therapeutic effect of a drug tested in primary SjS, although this would require a greater number of patients randomised than those included in reported trials.

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Box 1 Research agenda

- Is there a specific, differentiated treatment of lymphomas related to SjS?
- Is combination therapy a potential intervention to explore in SjS?
- Exploring targeted therapies against Th17 cytokines, IFNα, RORγt expression, Janus kinases (JAKS), STATs and mTOR intracellular pathways or interleukin-1.
- Searching for predictive factors of biological response.
- Potential use of sequential or intralesional use of biological therapies.
- Encouraging the development of new and innovative therapies.
- In what proportion of systemic patients is induction therapy with current therapeutic options effective in inducing sustained remission?
- Is the use of immunosuppressive and biologic agents safe and efficacious in the absence of concomitant glucocorticoid treatment?
- How safe and efficacious is the off-label use of other biologics after rituximab has failed?
- Can we find predictors of differential response to the synthetic and biological drugs used in SjS?
- Can we predict who will maintain remission after withdrawal of glucocorticoids?
- Will we be able to develop precision (personalised, stratified) medicine approaches in SjS? (IFN signature +/-; immunological or histopathological markers +/-)?
- Which biomarkers will help identify better predictors of poor outcomes?

In conclusion, the 2019 EULAR recommendations are based on the recent evidence collected on the management of primary SjS patients and on discussions by a large, broadly-based international TF. The recommendations synthesise current thinking on SjS treatment in a set of overarching principles and recommendations. These have been informed by a specific SLR on the efficacy and safety of topical and systemic interventions, although the high-quality scientific evidence focused on primary SjS patients fulfilling the currently-accepted sets of criteria was limited. However, the TF is convinced that adhering to these recommendations, including shared decision-making, assessing disease activity regularly with the ESSDAI instrument, and applying the sequence of drugs as proposed, will improve overall outcomes in a clear majority of patients with SjS. New research information on treatment strategies, predictive markers and other aspects will soon become available and will probably require an update of the recommendations in coming years (see Future Agenda box 1). Until then, we hope that the current recommendations will be broadly applied in clinical practice and/or serve as a template for national societies to develop local recommendations.

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Acknowledgements The Task Force gratefully acknowledges the financial support from EULAR and the support of the EULAR Standing Committee on Clinical Affairs (Prof. Ulf Müller-Ladner). The Task Force also expresses its sincere appreciation and gratitude to Désirée van der Heijde for her methodological suggestions and to the EULAR Secretariat and especially to Patrizia Jud, executive assistant, for the outstanding organisation. The authors also wish to thank David Buss (BA, Medical Writer) for technical assistance. Simon Bowman's salary is part funded by the Birmingham Biomedical Research Centre. These recommendations are also endorsed by the European Reference Network (ERN) for rare and low prevalence complex diseases ReCONNET (Rare Connective and Musculoskeletal Diseases Network).

Contributors PB-Z and SR performed the systematic literature review (SLR); MR-C and PB-Z drafted the manuscript. BK supervised the methodology of the SLR and the Delphi process. All authors edited the manuscript and accepted its final form.

Funding This study was funded by European League Against Rheumatism.

Competing interests MR-C reported consultancy for BMS, Gilead; FB reported consultancy GSK, UCB, ONO, Roche; MB consultancy and/or unrestricted grants from Medimmune, Amgen, GSK, Janssen, AbbVie; SB Participation in Abbvie Advisory Board; RP for Abbvie, Novartis, Ab2 Bio ltd, Celltrion healthcare; RC: speaker's and/or consultation fee from: Abbvie, BMS, Celgene, Gilead, Janssen Cilag, Lilly, MSD, Novartis, Pfizer, Roche and Sanofi; MR reported consultancy for Abbvie, BMS, Celgene, Janssen Cilag, Novartis, Pfizer, Roche and Sanofi; W-FN reported consultancy for GSK, Novartis, BMS, MedImmune and Abbvie; AGT reported Research Grants From Pfizer, Novartis, Abbvie, Genesis, GSK, Janssen, Eli-Lilly, Through The Research Accounts Of The University Of Athens; CHS: Consultant for Novartis in 2018; PW consultant for Roche, Novartis, Pfizer, Abbvie, Lilly, Gedeon-Richter, Sandoz, Medac, MSD, Sanofi-Aventis. TM reported consultancy Novartis; BAF reported consultancy for Novartis, Roche, MedImmune, BMS.

Ann Rheum Dis: first published as 10.1136/annrheumdis-2019-216114 on 31 October 2019. Downloaded from http://ard.bmj.com/ on February 3, 2023 by guest. Protected by copyright.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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RHEUMATOLOGY

Rheumatology 2017;56:e24–e48
doi:10.1093/rheumatology/kex166

Guidelines

The British Society for Rheumatology guideline for the management of adults with primary Sjögren's Syndrome

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Key words: Sjögren's, guideline, management, sicca

GUIDELINES

Background

Primary Sjogren's Syndrome (pSS) is a classic, immune-mediated, condition of unknown aetiology characterized by focal lymphocytic infiltration of exocrine glands [1]. Patients characteristically complain of drying of the eyes and mucosal surfaces along with fatigue and arthralgia. There is an association with autoimmune thyroid disease, coeliac disease and primary biliary cirrhosis. Systemic features include inflammatory arthritis, scLE, immune thrombocytopenia (ITP), vasculitis with purpura, salivary gland inflammation, neuropathies, interstitial lung disease (ILD) and a 5–10% lifetime risk of B cell lymphoma [2, 3].

This guideline reviews the treatment of the glandular and systemic features of pSS The management of the glandular features includes conserving, replacing and stimulating secretions. Systemic features may require system-specific therapy and immunomodulatory treatment. Holistic

NICE has accredited the process used by the BSR to produce its guidance for the management of primary Sjögren's Syndrome in adults. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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Submitted 7 September 2016; revised version accepted 20 March 2017

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management is important and many patients benefit from non-pharmacological therapies and general support.

Diagnosis

Patients commonly present with dryness of the eyes [4] and mouth [5]. In the early stages they may complain of grittiness rather than dryness of the eyes, and the mouth symptoms may require prompting. Fatigue and arthralgia are almost universal. There is often a considerable delay between symptom onset and diagnosis. The most widely accepted current classification criteria for pSS and those referred to in this guideline are the American-European Consensus Group (AECG) criteria [6]. The 2016 ACR–EULAR criteria have just been published [7] derived from criteria proposed by the Sjögren's International Collaborative Clinical Alliance (SICCA) [8]. The populations described by both criteria are very similar.

For a definite diagnosis the AECG criteria require four out of six of dry eye symptoms, dry mouth symptoms, objective ocular dryness (Schirmer's test $\leqslant$5 mm in 5 min or van Bijsterveld score $\geqslant$4), objective oral dryness (unstimulated salivary flow rate $\leqslant$0.1 ml/min or positive salivary scintigraphy and sialography), positive anti-Ro/La antibodies, labial gland focus score $\geqslant$1 including at least one of the last two objective features.

The 2016 ACR–EULAR classification criteria are based on the weighted sum of five items and require a total score $\geqslant$4 to meet the criteria for diagnosis where the presence of anti-Ro antibodies or focal lymphocytic sialadenitis with a focus score of $\geqslant$1 score 3 each and where abnormal ocular staining score $\geqslant$5, Schirmer's test result of $\leqslant$5 mm/5 min and unstimulated salivary flow rate of $<$0.1 ml/min score 1 each.

Investigations

The best-described autoantibodies in pSS are the anti-Ro and anti-La antibodies, which are routinely identified as part of the ENA laboratory screen. About two-thirds of patients with primary SS have anti-Ro antibodies and/or anti-La antibodies. These figures, however, depend on the classification criteria used, referral bias and access to labial gland biopsy.

Need for guideline

pSS typically presents in women in their fifth or sixth decade, although up to 10% of cases occur in men and it is also seen in younger people. Studies using the AECG criteria have estimated the prevalence in women in the UK at 0.1–0.4% [9]. Patients present to primary care physicians, general physicians, ophthalmologists and dental practitioners many of whom lack specialist knowledge regarding the treatment of this patient cohort.

Objective of guideline

This document aims to provide a pragmatic, practical guideline for the management of adults with pSS.

Target audience

The target audience includes rheumatologists, general physicians, general practitioners, specialist nurses and other specialists (e.g. ophthalmologists, dental practitioners and ENT specialists) who will review patients with pSS during their clinical practice. The guideline should also be of relevance to specialist registrars in training and specialist nurses.

Areas not covered

The management of children with SS is not specifically covered by this guideline although the general management of children and teenagers with SS is similar to that for adults with special emphasis on the importance of good dental care and hygiene to preserve dental health.

SS is very rare in teenagers and there are only anecdotal reports worldwide of its occurrence in pre-pubertal children so we would recommend that children and teenagers presenting with symptoms suggestive of SS are referred to a specialist centre for evaluation and treatment.

In addition this guideline does not cover the detailed management of patients with secondary Sjögren's. Where patients have secondary SS their systemic management should address the primary disease but the advice on topical management contained in these guidelines is applicable to sicca symptoms from any cause. This guideline does not cover the detailed management of patients with lymphoma, who should be managed in conjunction with oncologists and haematologists.

Stakeholder involvement

The multidisciplinary team involved in producing these guidelines was led by Dr Elizabeth Price, Consultant Rheumatologist, who chaired the team, undertook the systematic review and led the development of the guideline. The management of eye disease was led by Miss Saaeha Rauz, Clinical Senior Lecturer and Clinical Ophthalmologist, who also acted as The Royal College of Ophthalmologists' representative. Dr Anwar Tappuni, Reader and Academic Lead for Oral Medicine, was the main contributor to the oral section and Dr Nurhan Sutcliffe, Consultant Rheumatologist, acted as the lead for the systemic section. Ms Katie L. Hackett was the British Health Professionals in Rheumatology's representative and lead for non-pharmacological management. Dr Francesca Barone, Clinician Scientist and Honorary Consultant Rheumatologist, was the lead for the Delphi process and supervised Dr Guido Granata, Visiting Fellow, who undertook the Delphi analysis. Professor Wan-Fai Ng, Consultant Rheumatologist, Dr Benjamin A. Fisher, Senior Clinical Lecturer and Honorary Consultant Rheumatologist, Dr Michele Bombardieri, National Institute for Health Research Senior Clinical Lecturer in Rheumatology, Dr Elisa Astorri, Clinical Research Fellow, Miss Genevieve Larkin, Consultant Ophthalmologist, and Professor Simon Bowman, Consultant and Honorary Professor of Rheumatology, provided further review and clinical input. Mrs Bridget Crampton contributed as a patient representative and Dr Benjamin Empson provided GP representation.

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Conflict of interest statement

Any conflicts of interest among members of the working party were fully declared. The declared conflicts of interest are included at the end of the article.

Rigor of development and limitations

A search was undertaken for all relevant evidence in the Cochrane Library, MEDLINE (Ovid and PubMed) and EMBASE from 1990 to current (February 2015 and updated September 2015). Additional references were added through regular updates to the draft recommendations up to January 2016. Non-English language papers were excluded unless a translation was published. We also excluded treatments not currently available in the UK unless there was a significant likelihood they would become available in the near future. Identified papers were reviewed, categorized and the level of evidence graded according to international criteria from Ia through to IV and A through to B [10]. See supplementary data Search history and supplementary table S1, available at *Rheumatology* online, for full details of search criteria and level of evidence definitions.

The guideline was developed in line with the BSR Guideline Protocol using Appraisal of Guidelines for Research and Evaluation II methodology (http://www.agreetrust.org/). The wording and content of the recommendations were subjected to a formal Delphi process [11] using online surveys to determine the eventual strength of agreement (SOA) for each recommendation. The Delphi method was developed in the 1950s. It describes a process whereby a group of experts anonymously reply to questionnaires and subsequently receive feedback in the form of a statistical representation of the group response, after which the process repeats itself. The goal is to reduce the range of responses and arrive at something closer to expert consensus. In our case each recommendation was rated on a score from 1 (no agreement) to 10 (complete agreement). The results were collated and circulated to the group prior to the second round. We then included recommendations with a mean SOA score of $\geqslant 7$ plus $\geqslant 75\%$ respondents scoring $\geqslant 7$. This is expressed as the mean score with percentage $\geqslant 7$ in parentheses, for example, SOA 7 (75%) with a maximum of 10 (100%).

The guideline

Eligibility criteria

This guideline is primarily aimed at the management of patients with pSS as defined by the AECG [6] or ACR–EULAR (in press) criteria but the advice on topical management contained in these guidelines is applicable to sicca symptoms from any cause.

Exclusion criteria

Sicca symptoms can result from a variety of causes, some of which may be reversible if addressed. Drugs are a common cause of sicca and many different drug groups have been implicated. Potential causative agents include those with anti-cholinergic activity such as anti-depressants, anxiolytics and anti-psychotics; muscarinic anatagonists such as tamsulosin hydrochloride and ipratropium hydrochloride; anti-histamines; opiates; anti-hypertensives including beta-blockers and angiotensin converting enzyme (ACE) inhibitors; and proton pump inhibitors such as omeprazole. Avoiding these entirely may not be practicable, but use should be minimized in the presence of sicca symptoms if possible.

Sicca symptoms are commonly seen following head and neck radiotherapy and may respond to topical treatment and pilocarpine (see below). Dehydration and acute anxiety may cause temporary sicca symptoms. Rarely, primary salivary gland pathology other than SS including sarcoidosis, IgG4 disease [12] and graft *vs* host disease [13] may be implicated. Salivary gland aplasia and ductal atresia [14] are both rare causes of oral sicca and viral infections including hepatitis C and HIV can cause salivary gland disease with hypertrophy and sicca symptoms.

Xerostomia can be a feature of oral dysaesthesias with no objective reduction in salivary flow rate. Oral dysaesthesia or burning mouth syndrome is a chronic pain condition currently classified as a neuropathic disorder. Such patients may complain of a constellation of oral symptoms, including burning sensations, unusual taste as well as oral dryness, and their symptomatology is not uncommonly associated with anxiety states and clinical depression. There may also be a history of low back pain, FM and irritable bowel syndrome [15].

A syndrome comprising histological evidence of sialadenitis, nodular osteoarthritis and xerostomia has been described [16], but in view of the frequency of the individual clinical features and the demographics of the individuals with these conditions, clustering of these entities could also be expected to occur on a simple statistical basis.

Ageing *per se* is not a cause of xerostomia. Although there is a broadly linear reduction in the amount of functional acinar tissue within the salivary glands over time, this does not lead to clinically significant salivary gland hypofunction in normal subjects [17]. Xerostomia in the ageing population is more a function of intercurrent disease and medication rather than loss of secretory ability [18].

The guideline

The guideline covers management of the eye and mouth manifestations, systemic dryness and systemic disease in general with comments on the management of pregnancy and lymphoma in patients with SS. For each section we have reviewed and summarized the available evidence and then listed the recommendations that achieved a mean SOA score of $\geqslant 7$ plus 75% of respondents scoring $\geqslant 7$ after the second round of the Delphi process as described above. In general we would recommend initial symptomatic treatment of sicca manifestations combined, if appropriate, with systemic management.

Treatment of sicca manifestations

All patients with pSS (and sicca from other causes) should be offered symptomatic treatment of dryness. The sicca

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Table 1 Dry eye management summary

Level 1: mild dry eye	Level 2: moderate dry eye	Level 3/4: severe dry eye (ophthalmology only)
Features	Features	Features
Tear film break-up time: >9 s	Tear film break-up time: 5–9 s	Tear film break-up time: <5 s
Staining: VB score = 0–3, OSS = 0	Staining: VB score = 4–5, OSS = 1–6	Staining: VB score = 7–12, OSS = 5–12
Management	As for mild plus:	As for moderate plus:
Educational and environmental	Moisture chamber spectacles	Lubricants
Lubricants	Lubricants	High concentration hyaluronates 0.2–0.4%
Hypromellose	Carmellose 1% eye	Hyaluronates with Xanthan gum
Carbomer gels	Low concentration hydroxypropylguar eye drops	Soybean with phospholipids
Carmellose 0.5%	Sodium hyaluronate eye drops 0.1–0.18%	Mucolytics for filaments, e.g. acetylcysteine
Ointments	For corneal inflammation consider prednisolone 0.5% non-preserved 2–3× daily (ophthalmology only)	Higher strength topical steroids for short term use, e.g. dexamethasone 0.1%
Lid hygiene	For blepharitis consider metallomatrix proteinase inhibitors, e.g. doxycycline 50 mg od (ophthalmology only)	Ciclosporin-containing drops or ointment
Liposomal sprays available over the counter to replace tear film oil layer	Punctal plugging—punctal or intracanalicular plugs (ophthalmology only)	Nutritional tear substitutes
	Secretagogues	Autologous or allogeneic serum eye drops (available via specialist commissioned centres only)
	Oral pilocarpine max 5 mg 4× per day (start with 2.5 mg od and build up)	Permanent punctal occlusion via cautery of all four puncta
	Pilocarpine 4% (3 drops = 5 mg) for those who are unable to swallow (palliative care pathway [56])	Periorbital botulinum toxin for significant blepharospasm
		Bandage contact lenses
		Amniotic membrane overlay or corneal grafting for significant corneal ulceration and corneal melt or perforation

Based upon the DEWS workshop and the Meibomian Gland Dysfunction Workshop [19]. VB: van Bijsterveld Schema; OSS: ocular surface staining score.

symptoms classically affect eyes and mouth but many patients also experience a chronic, dry cough due to drying of the mucosal surfaces and, in women, vaginal dryness. In general treatment of sicca symptoms should aim to conserve, replace and stimulate secretions while reducing inflammation.

Management of ocular manifestations of SS

Dry eyes may be classified as mild, moderate or severe based on the presence of both symptoms and signs [19]. Definitions are included in Table 1 and rely on knowing the tear film break-up time and/or the ocular surface staining score. In the past, staging of eye disease has not routinely been carried out by optomoterists and ophthalmologists but this is changing with routine staging being introduced for other eye diseases. In practice rheumatologists and GPs will either rely on patient reported symptoms or simple Schirmer's testing to assess severity of disease but, by definition the majority of patients with SS will have severe dry eye (Schirmer's $\leqslant$5 mm in 5 min and tear break-up time $\leqslant$5 s).

It should be remembered that in Sjögren's associated dry eye all three layers of the tear film are affected. There is mucosal layer deficiency, aqueous deficiency and meibomian gland deficiency, all of which need to be addressed.

Ocular—conservation of tears and meibomian gland secretions

Systemic medications that exacerbate dryness should be avoided if possible. These include those with anti-cholinergic activity (psychotropics including antidepressants, anxiolytics and anti-psychotics), muscarinic antagonists (e.g. tamsolusin hydrochloride; ipratropium hydrochloride), anti-histamines, opiates, anti-hypertensives (e.g. beta blockers; ACE inhibitors) and proton pump inhibitors (e.g. omeprazole), although the latter may have an important role in the treatment of laryngotracheal reflux.

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Studies have shown that humidification of cabin air increases tear-film stability [20] in normal individuals and by extrapolation it is advised for dry eye. Patients consistently report feeling more comfortable in a humidified environment.

Two randomized placebo controlled trials showed improvements in symptoms of dry eye following oral supplementation with omega 3 fatty acids, with improvement in both Schirmer's test and markers of ocular inflammation [21, 22]. There is some low quality evidence that omega 7 derived from sea buckthorn oil provides some symptomatic relief of dry eye symptoms from both a small, open label, informal study [23] and a double-masked, randomized, parallel trial [24]. The evidence was felt to be of insufficient strength to include this as a recommendation within the final guideline.

Adequate meibomian gland secretion is essential to prevent evaporative tear loss. There is evidence that it is useful to enhance meibomian gland secretion using either warm compresses or commercially available microwavable lid warming compresses [25]. Patients should be advised to perform lid hygiene if required using proprietary wipes (available over the counter) or with a weak solution of bicarbonate. Useful guides for patients are available on both the National Health Service and the National Institute for Health and Care Excellence (NICE) websites [26, 27].

A recent report by the American Academy of Ophthalmologists reviewed the evidence for the oral antibiotics doxycycline, minocycline and azithromycin in the management of ocular surface disease arising from disorders of the meibomian glands. They identified eight studies that documented an improvement in meibomian gland-related ocular surface disease after treatment with these agents, although side effects were common. Only one study was a randomized, controlled trial. They concluded oral antibiotics may be an effective treatment for ocular surface disease that results from meibomian gland disease [28]. Two small observational, open label clinical studies of topical azithromycin ophthalmic solution 1% (twice daily for 2 days and once daily on days 3–28) in subjects with symptomatic meibomian gland disease, but not specifically SS, showed improvement in both clinical signs and symptoms of disease [29, 30]. Expert advice in the UK is to consider doxycycline 50 mg od for a minimum of 3 months in patients with persistent meibomian gland inflammation and blepharitis not responding to topical management. If treating young patients it is important to remember that doxycycline is contraindicated in those $<$12 years of age. Minocycline is avoided because of the small risk of causing drug-induced lupus.

Wearing spectacles reduces surface evaporation of tears by up to 30% and the effect can be optimized by the use of moisture chamber spectacles [31, 32]. The latter can be manufactured by opticians or purchased on-line. There is evidence supporting the early use of punctal plugs [33, 34], which improve symptoms of dry eye significantly more than artificial tears alone.

First line treatment should be with visible plugs. If this successfully improves symptoms or signs, and there is no evidence of excess watering or over flow of tears, then permanent punctal occlusion can be achieved with punctal cautery. Intracanalicular plugs are effective but increase the risk of granuloma and infection [35, 36] and are not visible on examination. Referral to an ophthalmologist is advised and it is important to remember that plugs are available in different sizes and the puncta should ideally be measured with a calliper prior to selection and insertion of an appropriately sized plug. Improperly sized plugs may fall out, with accompanying deterioration in symptoms; alternatively loose plugs will allow tear flow, or cause irritation.

Recommendations for conservation of tears and meibomian gland secretions

(i) Treatment should begin with conservation of tears by humidification and avoidance of systemic medication that exacerbates dryness. Level of evidence Ib/A; SOA 8.9 (97%).
(ii) Patients should be advised to stimulate meibomian gland secretion daily using either warm compresses or commercially available microwavable lid warming compresses or other devices and perform lid hygiene if required using proprietary wipes (available over the counter) or with a weak solution of bicarbonate. Level of evidence III/C; SOA 8.9 (93.3%).
(iii) In patients with persistent meibomian gland inflammation and blepharitis, treatment with doxycycline 50 mg od for a minimum of 3 months may be effective. Level of evidence IV/D; SOA 8.83 (92.9%).
(iv) Early referral to an ophthalmologist for review and consideration of insertion of punctal plugs or cauterization of puncta is recommended. Level of evidence II/B; SOA 9.27 (100%).

Ocular—replacement of tears and meibomian gland secretions

Liposomal sprays (available over the counter but not currently FP10 prescribable) reduce evaporative tear loss and replace the meibomian gland layer and have been shown to significantly reduce sicca symptoms [37].

To replace the aqueous tear film start with simple lubricating drops using the most cost-effective options. In general start with low viscosity simple drops such as hypromellose and escalate as symptoms dictate. Given the severity of dry eye disease in primary SS, it is unlikely, however, that simple drops will be sufficient to control the disease. When prescribing take into account the bottle or device used to apply the drops. In particular consider ease of application and expiry dates. See advice below and in accompanying Table 2 for preparations.

Multi-use ophthalmic preparations rapidly become colonized with bacteria and are associated with high rates of pathogenic organisms on conjunctival culture [38]. As a result, the majority of multi-dose preparations contain a preservative to limit bacterial, fungal and amoebic ocular infections and prolong shelf life by preventing biodegradation. High concentrations of certain preservatives

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Table 2 Dry eye topical therapies

Viscosity	Compound	Preserved	Non-preserved
Low	Hypromellose	Hypromellose MD[a]	Artelac SDU
		Xailin Hydrate MD	Hydromoor SDU
		Tears Naturale MD[a]	Tears Naturale SDU
			Tear-Lac MD
	Polyvinyl alcohol	Liquifilm Tears MD[a]	Liquifilm Tears SDU
		Tubilux MD	Refresh SDU
Thin–medium	Carbomers	Viscotears	Viscotears SDU
		Gel Tears[a]	Visidic[b]
		Clinitas Carbomer Gel	
		Artelac Nighttime Gel	
	Carmellose	Optive 0.5% MD	Celluvisc 0.5 or 1% SDU
		Carmize 0.5% MD	Xailin Fresh 0.5% SDU
		Lumecare Advance 0.5% MD	Evolve Carmellose 0.5% MD
			Carmize 1% MD
	Guar gums	Systane MD	Systane SDU,
		Systane Ultra	Systane Ultra SDU
		Systane Gel	
		Systane Balance	
Thick–medium	Sodium hyaluronates	Xailin HA 0.2%	Vismed 0.18% SDU or MD
		Blink Intensive Tears 0.2% MD	Vismed gel 0.3%
			Clinitas 0.4% SDU
		Optive Fusion 0.1% MD	Clinitas Multi 0.4% MD
		Oxyal 0.15% MD	Hycosan[b]
		Artelac Rebalance 0.15% MD	Hylo-Forte 0.2%, Hylo-Care 0.1%, Hylo-Tear 0.1% (MD) Artelac Splash 0.2% SDU Blink Intensive 0.2% SDU Evolve Hyaluronate 0.4% MD Lubristil 0.15%/1% xanthan gum
High	Paraffin/white petroleum	—	Lacri-lube
			VitA-Pos
			Xailin Night
			HydraMed Night
Others	Liposomes[b]	—	Actimist[b]
			Vizulize Dry Eyes Eye Mist[b]
			Eye logic liposomal eye drops and spray (formerly Clarymist)[b]
	Soy bean/mineral oil	—	Emustil SDU
	Mucolytics[c]	Aceylcesteine (Ilube)[c]	Acetylcysteine 10% MD (unlicensed)[c]
	Anti-inflammatory or immune regulators[c]	—	Ciclosporin 0.2% (unlicensed, Optimmune®) veterinary preparation[c]
			Restasis® (not licensed EU)[c]
			Ciclosporin 0.1% (licensed, Ikervis® SDU)[c]
	Disaccharides[b]	—	Thealoz MD[b]
			Thealoz Duo MD[b]
			Thealoz Duo SDU[b]
			Thealoz Duo Gel SDU[b]
			HydraMed [sodium hyaluronate (0.2% w/v), polysaccharide (0.2% w/v)]

A selection of ocular lubricants available in preserved and non-preserved forms. Most are available both over the counter and on prescription, some are prescription only and others are over the counter only. [a]Contains benzalkonium chloride (should be avoided). [b]Over the counter only. [c]Prescription only. MD: multidose bottle; SDU: single dose units.

may damage and irritate ocular tissue and this effect is enhanced in those with ocular surface disease. Benzalkonium chloride is the most frequently used preservative in topical ophthalmic preparations and its epithelial toxic effects are well established [39]. Preserved preparations should be avoided in patients using eye drops long term (for >3 months), instilling drops >4 times daily or those with ocular surface disease (effectively the majority

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of patients with pSS). Some eye drops are available as single-use preservative-free preparations. Although convenient these are often costly and require good manual dexterity to use. Increasingly eye drops are available in multi-use bottles with preservative systems that biodegrade on contact either with light or with the ocular surface. Other preservative-free multidose systems use a pump or vacuum system preventing regurgitation into the bottle and obviating the need for preservatives altogether.

Autologous or allogeneic serum eye drops are the only available nutritional tear substitutes and are effective and well tolerated by patients [40, 41]. However, they are very expensive to produce and are only available from commissioned specialist centres.

Recommendations for replacement of tears and meibomian gland

(i) Recommend liposomal sprays to reduce evaporative tear loss and replace the meibomian gland layer. Level of evidence III/C; SOA 8.29 (92.8%).
(ii) Start with simple lubricating drops using the most cost-effective options (see Table 2 for preparations). Level of evidence IV/D; SOA 9.3 (93.3%).
(iii) Avoid preservative-containing preparations. Level of evidence I/A; SOA 9.21 (92.9%).
(iv) Patients with severe dry eye, not responding to conventional treatment may be referred to specialist centres for consideration of autologous or allogeneic serum eye drops. Level of evidence IIb/B; SOA 9.5 (100%).

Ocular—anti-inflammatory

There is evidence supporting the use of topical anti-inflammatories under ophthalmic supervision in patients with persistent corneal inflammation. Low dose steroid-containing eye drops are recommended for short term use and have been shown to be both safe and effective [42]. Longer term use of topical steroids has been associated with an increased risk of glaucoma and cataract and should be avoided [43]. In general the use of topical steroids should be limited to patients under supervision by an ophthalmologist. For longer term use ciclosporin-containing eye drops have been shown to reduce subjective symptoms and improve objective signs of inflammation in patients with both primary and secondary SS [44–46]. Ciclosporin 0.1% (Ikervis®) is licensed and NICE approved as a possible treatment for people with dry eye disease that has not improved despite treatment with artificial tears (NICE TAG 369 December 2015 [47]) but must initially be prescribed by a sub-specialty ophthalmologist. An unlicensed veterinary ointment (Optimmune®, ciclosporin 0.2%) or a preservative-free eye drop available via Moorfields Pharmaceuticals may be used as alternatives. All forms of topical ciclosporin may be used off licence for patients <16 years of age.

Topical NSAIDs such as diclofenac and indomethacin have been shown to improve ocular discomfort but reduce corneal sensitivity and may predispose to further corneal damage and should therefore be used only with caution in patients with SS [48, 49].

Recommendation for anti-inflammatory treatment of dry eye

(i) Low dose steroid-containing eye drops are recommended for short term use under ophthalmic supervision only. Level of evidence Ib/A; SOA 9.64 (100%).
(ii) Longer term use of topical steroids should be avoided. Level of evidence Ib/A; SOA 9.64 (100%).
(iii) Ciclosporin-containing eye drops or ointments may be used under ophthalmic supervision in patients with evidence of chronic inflammation. Level of evidence Ib/A; SOA 9.38 (100%).
(iv) Topical NSAIDs such as diclofenac and indomethacin should be used with caution under ophthalmic supervision only. Level of evidence IIb/B; SOA 9.86 (100%).

Ocular—stimulate

Oral pilocarpine treatment can improve ocular dryness and tear film break-up time and increase goblet cell density thus improving the mucous layer [50–54]. Symptomatic and objective improvements are seen in more than a third of patients, although side effects (headache, increased sweating) may limit its use in some.

The recommended starting dose is 5 mg once daily, escalating at weekly intervals as tolerated to 5 mg qds (with meals and at bedtime) but if response is insufficient, the dose can be increased to 30 mg daily, if tolerated well; discontinue if no improvement after 2–3 months. Contraindications include uncontrolled asthma and chronic obstructive pulmonary disease, uncontrolled cardiorenal disease and acute iritis. Common side effects include dyspepsia, diarrhoea, abdominal pain, flushing and increased urinary frequency. There is evidence from an observational study that it is both safe and effective in children and young people as young as 9 years of age [55]. In patients intolerant of pilocarpine tablets, using topical ocular drops orally allows delivery of a smaller dose of drug and may be better tolerated. The Palliative Care Formulary suggests 2–3 drops of pilocarpine 4% eye drops is equivalent to 4–6 mg oral pilocarpine; however this is an off-licence use [56].

Recommendations for stimulation of ocular secretions

(i) A trial of pilocarpine 5 mg once daily increasing stepwise to 5 mg qds is recommended for patients with significant sicca symptoms and no contraindications to its use. Level of evidence IIb/B; SOA 9.08 (92.3%).

Miscellaneous treatments for dry eye and ocular complications

Mucolytic eye drops, for example, acetylcysteine 5–10% non-preserved, are useful for patients with mucous threads or ocular surface filaments [57] and have also

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been shown to improve tear break-up time and Schirmer's tests in patients with meibomian gland disease [58].

Some patients with severe dry eye develop an associated blepharospasm. There are small case series describing a good response to botulinum toxin injections in these circumstances [59, 60].

For severe dry eye bandage scleral contact lenses, designed to protect the surface and create an optimized environment for healing, may be indicated. These lenses vault over the corneal surface and rest on the sclera. They are rigid and gas-permeable and require specialist fitting and manufacture. They are only available in specialist centres for severe corneal disease refractory to other treatment measures. A number of studies have shown significant decreases in corneal staining with scleral contact lens wear with significant improvements in dry eye symptoms and quality of life [61–63].

Corneal grafting or amniotic membrane overlay may occasionally be indicated for cases of significant corneal ulceration and corneal melt [64]. Neuropathic pain (when dry eye symptoms outweigh clinical findings) is a recognized entity. Neuropathic pain strategies should be considered for these patients [65].

Recommendations for severe, complicated dry eyes

(i) Mucolytic eye drops should be prescribed for patients with mucous threads or ocular surface filaments. Level of evidence III/C; SOA 9.38 (100%).
(ii) Patients with severe dry eye and associated blepharospasm may benefit from referral to a specialist centre for consideration of botulinum toxin treatment. Level of evidence III/C; SOA 9.17 (100%).
(iii) Patients with severe dry eye and corneal ulceration, not responding to conventional treatment, may be referred to specialist centres for consideration of bandage contact lenses or amniotic membrane grafting or corneal grafting for perforations. Level of evidence III/C; SOA 9.15 (92.9%).

Management of oral manifestations of SS

Dry mouth (xerostomia) is a hallmark of pSS and the majority of patients suffer from both reduced salivary flow rate and increased viscosity of saliva due to relative deficiency of the aqueous component, which may compromise oral health.

Complications of long-term xerostomia include oral discomfort and soreness and a burning sensation in the mouth. An increased rate of dental caries, excessive tooth wear and premature tooth loss are often observed. Patients struggle to achieve a high standard of oral hygiene and may suffer from halitosis. Patients tolerate dentures poorly and often complain of difficulty retaining them in the mouth with sore, ulcerated gums as a consequence of rubbing. Many patients suffer recurrent infections including parotitis, intraoral candidiasis and angular cheilitis. Dysarthria, dysphagia and dysgeusia (distorted sense of taste) are seen in established disease.

The evidence surrounding periodontal disease in Sjögren's is conflicting, with some studies suggesting an increased prevalence of periodontal disease [66] but others not [67].

Effective management of the dry mouth is important for the maintenance of oral health and to improve oral health-related quality of life as well as general health and quality of life.

Oral—conserve

Many patients with pSS anecdotally report improvement in symptoms following humidification of room air and patients frequently report worsening of symptoms in dry and air-conditioned environments.

Patients with pSS have higher rates of the cariogenic bacterium *Streptococcus mutans*, dental caries and dental loss compared with controls despite apparently good dental care [68, 69]. Dental caries is considered to be a diet-mediated disease, as sugars are essential in the caries process. This has been confirmed in several large-population-based studies that have shown a significant association between total sugar intake and the development of dental decay over time in a normal population. Twice daily use of fluoride toothpaste reduced but did not eliminate the association between diet and dental decay in these studies [70–72].

Given their enhanced risk of dental decay patients with pSS should be advised to practice excellent oral hygiene and avoid sweetened food and drink on a regular basis. Assessment by an Oral Medicine specialist and/or regular visits to a general dental practitioner are recommended to monitor and treat the oral manifestations of SS with the emphasis on preventative dental care.

The optimum concentration of fluoride in standard toothpaste has been calculated assuming a normal salivary flow rate and taking into consideration the availability of fluoride in normal saliva. Concentrations of fluoride in standard over-the-counter toothpastes vary from 500 to 1000 parts per million (ppm) and occasionally higher. Prescription toothpastes contain fluoride concentrations of between 2800 and 5000 ppm. Dry mouth patients will need a higher concentration of fluoride in toothpaste to compensate for the lack of salivary fluoride. A number of studies [73–75] and a Cochrane review [76] have concluded that caries protection is increased with higher fluoride concentrations. A systematic review of the literature and a Delphi consensus exercise by a national panel of experts in North America concluded that there was good evidence that a prescription strength, home-use, fluoride gel or paste should be used in all patients with pSS [77].

Acidic products and those containing sugar should not be prescribed for dentate patients since maintaining a neutral oral pH environment may reduce the development of dental caries [78].

There is evidence that in addition to the total sugar content of the diet, frequency of sugar intake is implicated in dental decay [77]. In light of this we recommend that patients with pSS avoid food and drinks other than plain

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water between meals and from 1 h before bedtime and all through the night.

Patients should be advised to brush their teeth at least twice daily (but not immediately after eating) including before bed at night using a pea sized amount of high fluoride toothpaste and use fluoride-containing tooth mousse or gel on teeth twice daily. They should avoid alcohol-containing mouth washes, sugary or fizzy drinks and frequent snacking [77].

Chlorhexidine is an effective antiseptic that inhibits plaque formation on teeth and is useful for controlling gingivitis [79]. Many oral specialists and dentists recommend an alcohol-free chlorhexidine mouth wash in pSS patients as preventative treatment for gum disease. It can be used twice daily for a maximum of 2 weeks every 3 months but over use can lead to staining of teeth.

Recommendations for conservation of moisture and oral hygiene

(i) Patients should be advised to humidify the environment. Level of evidence IIV/D; SOA 9.13 (100%).
(ii) Patients should be advised to practice excellent oral hygiene, limit sugar intake and avoid food and drinks other than plain water between meals and from 1 h before bedtime and all through the night. Level of evidence IV/D; SOA 9.8 (100%).
(iii) Assessment by an oral medicine specialist and/or regular visits to a general dental practitioner typically at 3–6 monthly intervals are recommended to monitor and treat the oral manifestations of SS. Level of evidence IV/D; SOA 9.8 (100%).
(iv) Aim to avoid acidic products and those containing sugar when prescribing for dentate patients. Level of evidence IV/D SOA 9.87 (100%).
(v) Patients should be advised to brush teeth at least twice daily (but not immediately after eating) including before bed at night using a pea sized amount of high fluoride toothpaste and use fluoride-containing oral mousse or gel on teeth twice daily. Level of evidence I/A; SOA 9.8 (100%).
(vi) Alcohol-free chlorhexidine mouth wash used twice daily for a maximum of 2 weeks every 3 months can help prevent gum disease but over use can lead to staining of teeth. Level of evidence IV/D; SOA 9.0 (100%).

Oral—replace

It is common practice to manage mild symptoms by recommending that patients sip water, suck ice or chew sugar-free gum [77, 80]. More severe dryness can be managed with commercially available topical and systemic treatments for dry mouth.

Saliva substitutes provide symptomatic momentary relief of oral dryness. A Cochrane review of the effectiveness of topical treatments for dry mouth from any cause, including parallel and crossover randomized controlled trials of lozenges, sprays, mouth rinses, gels, oils, chewing gum and toothpastes did not find strong evidence for their effectiveness [81, 82], but in the experience of the working group patients report increased oral comfort from their use.

The ideal preparation will have neutral pH and contain fluoride and other electrolytes, mimicking the composition of natural saliva. Saliva substitutes are available commercially in the form of oral sprays, gels and rinses. Most are freely available over the counter and some are prescription only. The choice will depend upon patient preference and local availability. Fluoride-containing, neutral pH preparations should be prescribed for dentate patients (see Supplementary table S2, available at *Rheumatology* online, for products available in the UK). Preparations with acidic pH and/or without added fluoride should only be used in edentulous patients.

There is limited evidence that an oxygenated glycerol triester saliva substitute spray is more effective than a water-based electrolyte spray in older patients with dry mouth [83].

Patients with Sjögren's are at increased risk of frictional oral ulcers [84]. There is evidence that polyvinylpyrrolidone and sodium hyaluronate oral gel (Gelclair) may be helpful in patients with recurrent oral ulceration post-chemotherapy but no published studies of its effectiveness in SS [85]. A list of commercially available oral preparations is provided for reference in Supplementary table S2, available at *Rheumatology* online.

Recommendations for replacement of oral secretions

(i) Patients should be advised to use a neutral-pH fluoride-containing mouth wash, gel or spray as required for symptomatic relief. Level of evidence III/C; SOA 9.43 (92.8%).

Oral—stimulate

Topical saliva stimulants

Although no study directly links improved salivary flow to caries prevention, expert opinion acknowledges that increasing saliva flow is likely to reduce caries incidence in the longer term.

Chewing sugar-free gum increases saliva production and there is some evidence that in addition to its value as a non-sugar sweetener xylitol may have a role in caries prevention in its own right [86, 87]. A recent Cochrane review of the evidence for xylitol concluded that over 2.5–3 years of use, a fluoride toothpaste containing 10% xylitol may reduce caries by 13% when compared with a fluoride-only toothpaste, but that there was insufficient evidence to determine whether any other xylitol-containing products could prevent caries in infants, older children or adults [88].

Many patients chew or suck sugar-free sweets and report benefit, but there is no published evidence supporting this. Certain foodstuffs may be more effective at stimulating saliva than others, but acidic products and those containing sugar should be avoided because of their cariogenic potential. A small cross-over study in normal volunteers assessed the efficacy of yogurt and lemon juice as salivary stimulants and found that both were

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effective but yogurt more so than lemon juice compared with baseline, leading them to suggest that yogurt is a potential candidate for the treatment of dry mouth and warrants further study [89].

Some commercially available salivary stimulants are available in the UK. There is little convincing evidence of efficacy and conflicting results from the few reported studies [90, 91].

A small single-blinded, open-label, cross-over clinical study of a branded dry mouth product (Xerostom) containing olive oil, betaine and xylitol in a population with polypharmacy-induced xerostomia resulted in increased unstimulated whole salivary flow rates, reduced complaints of xerostomia and improved xerostomia-associated quality of life. No clinically significant adverse events were observed [92]. The preparation is non-acidic and contains both fluoride and calcium so may be suitable for patients with SS, although there are no published studies in this patient population.

Anhydrous crystalline maltose is available over the counter or on-line and has been shown to increase salivary flow rates with minimal adverse effects in small, observational studies [93] but is not available on prescription.

There is some experimental evidence for both acupuncture and mild electrical stimulation improving salivary flow rates. Published studies are generally small, usually observational and are not specifically looking at patients with SS [81]. There were adverse effects reported with the use of acupuncture, but these were mild and of short duration. There were no reported adverse effects from electrostimulation, with some evidence for improved salivary flow. Further larger studies are planned but neither is currently routinely available in the UK for the treatment of sicca [94]. A gel-releasing device (reservoir) worn in the mouth has been trialled and may be effective in some patients [95], but more research is needed.

Recommendations for mechanical stimulation of oral secretions

(i) Patients should be advised to chew xylitol-containing sugar-free gum. Level of evidence III/C; SOA 9.67 (100%).

Systemic stimulants

Pilocarpine hydrochloride (Salagen) is licensed for use in the UK for dry mouth and eyes in SS. It acts as an agonist on muscarinic-cholinergic receptors to stimulate secretion. It is effective in both primary and secondary SS. There are a number of randomized, controlled trials in patients with Sjögren's confirming significant symptomatic improvement and objective evidence of increased salivary flow in patients treated with pilocarpine [96–98]. Evidence suggests that at least half of patients respond although it can take up to 12 weeks to see a therapeutic benefit. In long term use levels of candida colonization reduce [99]. Side effects are common and dose dependent. They include sweating, palpitations and flushing. See 'Ocular—stimulate' section for more detail on the use of pilocarpine and adverse effects.

Cevimeline is another muscarinic agonist that stimulates fluid secretion generally [100, 101] but has higher affinity for muscarinic receptors located on lacrimal and salivary gland epithelium and may be associated with fewer side effects compared with pilocarpine [102]. However, this drug is not currently licensed for use in the UK.

There is some limited evidence that the H2 blocker nizatadine mildly improves (20% over baseline) objective and subjective measure of oral dryness and is well tolerated although it is not licensed for this indication in the UK [103].

Recommendations for systemic stimulation of secretions

(i) A trial of pilocarpine 5 mg once daily increasing stepwise to 5 mg qds is recommended for patients with significant sicca symptoms and no contraindications to its use. Level of evidence IIb/B; SOA 9.77 (100%).

Treatment of oral candida

Oral candida is a frequent problem in patients with Sjögren's-associated dry mouth [104] and patients have high levels of candida carriage despite good dental hygiene [105]. Patients may have visible white plaques (simple infection) or erythematous infection, when they present with a red, raw tongue or oral cavity. Clinical experience suggests that whereas topical agents such as nystatin may be adequate to treat simple infection, oral fluconazole is required to treat erythematous infection. The presence of dentures creates an environment where candida may become persistent.

Angular cheilits, where patients present with dry, fissured erythematous lesions in the corner of their mouths, is another manifestation of candidal infection in SS. It can be effectively treated with miconazole topically for 2 weeks, using a clean cotton bud to apply to each side to prevent cross-contamination and persistence of infection [106].

Recommendations for treatment of oral candida

(i) In simple candida infection (visible white plaques) treat with oral nystatin liquid 1 ml five times daily for 7 days. Consider repeating the treatment for 1 week every 8 weeks if frequent recurrence. If the patient has erythematous infection manifesting as a red, raw tongue or oral cavity and commonly seen in denture wearers, use fluconazole 50 mg od for 10 days. Level of evidence IV/D; SOA 9.86 (100%).

(ii) Treat angular cheilitis with miconazole topically for 2 weeks, using a clean cotton bud to apply to each side to prevent cross-contamination and persistence of infection. Level of evidence IV/D; SOA 9.86 (100%).

Management of salivary gland enlargement

Some patients with pSS have recurrent or persistent salivary gland enlargement. This may occur during disease

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activity flares or may reflect duct obstruction due to strictures, stones or inspissated secretions.

Parotid sialography is a very specific diagnostic test for pSS [107] that involves injection of contrast materials into the salivary ducts and is associated with a small risk of infection, ductal perforation and allergic reactions. Intraductal injection of contrast can assess the ductal system and exclude strictures [108]. Interventional sialoendoscopy has been reported to be useful in patients with SS with chronic obstructive sialadenitis unresponsive to medical therapy. Under local anaesthesia the orifice of the salivary gland is intubated and the scope advanced, with continuous saline lavage. This allows obstructing plaques to be washed out and any strictures dilated. Symptomatic improvement was achieved in 85% of patients using this technique [109]. However, sialoendoscopy is not widely available and no large scale or long term studies have been published.

In contrast salivary gland US is non-invasive, well tolerated by patients and easily repeatable. US allows assessment of the architecture of the major salivary glands and, used in conjunction with Doppler signals, it may help differentiate between benign and malignant lesions. In some centres salivary gland US is utilized as a diagnostic screening tool and studies confirm it has a high positive predictive value of 85% with good correlation between abnormalities on US and salivary gland histology [110]. Baseline ultrasound is recommended in patients with salivary gland swelling to look for active inflammation, infection and stones. Consider repeating the US if there is a history of new persistent or recurrent salivary gland swelling to monitor for disease progression and development of complications [111].

If there is acute inflammation in the absence of infection and stones then a short course of oral prednisolone or an intra-muscular injection of depomedrone (typically 120 mg) will often settle the glandular swelling promptly (anecdotal evidence). There is anecdotal evidence that massaging the glands can help reduce discomfort in chronically inflamed glands.

Recommendations for management of salivary gland enlargement

(i) Consider salivary gland US to look for active inflammation, infection and stones. Level of evidence IV/D; SOA 9.7 (100%).
(ii) If acute inflammation in the absence of infection and stones then a short course of oral prednisolone or an intra-muscular injection of depomedrone will often settle the glandular swelling. Level of evidence IV/D; SOA 9.01 (100%).
(iii) Massaging the glands can help reduce discomfort in chronically inflamed glands. Level of evidence IV/D; SOA 9.31 (92.8%).

Systemic dryness

Many patients report a chronic dry cough due to drying of mucosal surfaces. Humidification of inspired air is reported to help by some patients [112]. Pilocarpine improves secretions in general and anecdotally reduces the frequency and severity of dry cough. A mucolytic agent (i.e. carbocysteine) reduced the viscosity of sputum, improved the ability to cough up bronchial secretions, and reduced cough frequency and shortness of breath in a double blind controlled study of patients with chronic bronchitis [113]. There is anecdotal evidence it helps in patients with SS and an associated chronic, dry cough. Concomitant use of oral acetylcysteine with AZA and steroids should be avoided given evidence of increased hospitalization and death in a group of patients with pulmonary fibrosis (but not Sjögren's) treated with triple therapy *vs* placebo [114]. It should be remembered that chronic dry persistent cough may be a sign of ILD and should prompt appropriate investigations.

Females with SS frequently complain of vaginal dryness [115]. Pilocarpine may help this by non-specifically stimulating secretions. There is evidence supporting the use of non-hormonal moisturisers in the treatment of vaginal dryness from any cause [116–118]. Vaginal moisturizers applied on a regular basis have an efficacy equivalent to local hormone replacement for the treatment of local urogenital symptoms such as vaginal itching, irritation and dyspareunia [116]. Patients with SS have both vaginal dryness and atrophy of the genital skin [119]. There is evidence supporting the use of topical oestrogen-containing products in patients with post-menopausal vaginal atrophy and dryness [116]. Creams and pessaries are equally effective and although systemic absorption can occur with local preparations, there is no current evidence of an increased risk of endometrial thickening [116]. The use of local hormone replacement therapy can reduce the frequency of recurrent urinary tract infections in post-menopausal women [116].

Recommendations for management of systemic dryness

(i) A trial of pilocarpine 5 mg once daily increasing stepwise to 5 mg qds is recommended for all patients with significant systemic dryness and no contraindications to its use. Level of evidence IV/D; SOA 9.08 (92.3%).
(ii) Patients with vaginal dryness should be advised to use a non-hormonal vaginal moisturiser with or without a topical oestrogen-containing product. Level of evidence I/A; SOA 9.8 (100%).

Treatment of systemic disease

Systemic (extra-glandular) features are seen in ~70% of patients with SS and are severe in about 15% [120]. The most commonly involved organs are joints, lungs, skin and peripheral nerves [3]. Raynaud's and thyroid disease tend to be commoner in females and lung involvement and peripheral neuropathies are commoner in those with a disease duration of > 10 years [2]. Other systemic features may include autoimmune liver disease, renal involvement, scLE, ITP, myositis, monoclonal gammopathy of uncertain significance and lymphoma. There are also common overlapping conditions, most notably thyroid disease in up to

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20% [121], primary biliary cirrhosis in 8% [122] and coeliac disease in 4.5% [123].

Although significant systemic complications are more common in the Ro/La positive group [3] recent evidence suggests that systemic complications also affect a reasonable proportion of the antibody negative group with SS [124] suggesting that all patients with SS warrant consideration of active treatment.

Non-pharmacological interventions for systemic disease

A recent systematic review evaluated the evidence for non-pharmacological interventions for pSS and found that much of the evidence was inconclusive [125]. The available studies suggest that patients with SS benefit from moderate to high intensity exercise with improvements in aerobic capacity, fatigue scores, physical functioning and depression [126].

Lifestyle management strategies may benefit SS patients if fatigue is significantly affecting their ability to perform daily activities. Strategies recommended by NICE guidance for fatigue include sleep management, activity management, relaxation techniques, cognitive behavioural therapy and graded exercise therapy. See relevant NICE guidance on management of fatigue in adults.

Many patients report benefit from joining a Sjögren's support group. The British Sjögren's Syndrome Association provides information and advice for members via their website, a quarterly magazine and a dedicated telephone helpline (www.bssa.uk.net). Arthritis Research UK (www.arthritisresearchuk.org) provides helpful information and leaflets on SS, anti-rheumatic drugs and lifestyle advice.

Recommendations for non-pharmacological interventions for systemic disease

(i) Regular exercise and, where appropriate, a graded exercise programme are recommended for patients with SS presenting with fatigue. Level of evidence IIb/B; SOA 9.33 (93.3%).
(ii) Provide written patient information and details of appropriate support groups and on-line resources. Level of evidence IV/D; SOA 9.8 (100%).

Immunomodulation for systemic disease

Early and aggressive immunomodulation is recommended for RA and increasingly for other autoimmune diseases but not well established for SS. An evidence base is lacking and patients with SS often tolerate these drugs poorly. There is, however, increasing insight into the pathogenesis of SS and interest in its therapeutic management with an increase in the use of conventional disease modifying drugs and research interest in the development of targeted biological agents. The guideline working group considered the evidence supporting the use of corticosteroids, disease modifying drugs, biologics and other drugs alongside their own experience. Where disease modifying drugs are used they should be monitored in accordance with the recommendations of the latest BSR DMARD guidelines (in press). Biologics are not currently NICE approved or funded for the treatment of SS.

Systemic pulmonary manifestations of Sjogren's include ILD and cysts. Usual interstitial pneumonitis and non-specific interstitial pneumonitis are the most commonly reported. In general systemic steroids are recommended as first line treatment, then subsequently various immunosuppressives, including CYC and AZA, rituximab and anti-malarials depending on steroid responsiveness [127–129]. A broad range of neurological complications have been described in Sjögren's. A diffuse sensorimotor neuropathy, confirmed on nerve conduction testing, may affect $>15\%$ of patients with Sjögren's [130]. There are anecdotal reports of benefit from rituximab, immunoglobulins, AZA and HCQ [130].

Trigeminal neuropathy/neuralgia has been described in up to 5% of patients with Sjögren's. It does not usually respond to treatment with steroids and in general is treated as for trigeminal neuralgia of unknown cause. Mononeuritis multiplex is probably seen in $<3\%$ of Sjögren's patients over their lifetime. It is associated with vascultis and may respond to treatment with steroids and CYC [131]. Autonomic neuropathy is common and correlates with patient reported outcomes [132]. It may respond to simple, symptomatic treatment. SS myelopathy can mimic multiple sclerosis. Patients may present with paraplegia, sensory changes and bladder dysfunction. Steroids and CYC may be helpful [133].

Signal hyperintensities on brain MRI have been described in patients with Sjögren's and have been postulated to indicate the presence of an underlying cerebral vasculopathy [134]. Correlation with serological abnormalities and clinical symptoms is poor, however. Neuromyelitis optica spectrum disorder is associated with the presence of aquaporin-4 antibodies and although seen in association with Sjögren's may not be a direct neurological complication of Sjögren's. This patient group benefits from aggressive and ongoing immunosuppression [135].

Although significant renal impairment is rare, tubulointerstitial nephritis and, more rarely, immune complex glomerulonephritis are well described renal manifestations of Sjögren's. In those patients with tubulointerstitial nephritis there is a mononuclear lymphocytic infiltrate on renal biopsy, and treatment with mycophenolate and steroids improves the renal function [136].

Corticosteroids

Prednisolone has been shown to help systemic features including lung disease [127–129] cytopaenias [137], and, in combination with CYC or chlorambucil, neurological involvement [138, 139]. Small studies of low dose prednisolone (5–7.5 mg per day) have shown improvements in sicca symptoms and modest improvements in salivary flow [140].

There are no controlled trials of pulsed i.v. methylprednisolone or i.m. depomedrone in Sjögren's, although there are anecdotal reports of successful use of pulsed steroids in patients with Sjögren's associated lung disease [141], ganglionopathy [142], myelopathy [133] and renal involvement [143].

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Recommendations for corticosteroids

(i) Corticosteroids are not recommended for the routine treatment of pSS although intermittent short courses of oral or intramuscular steroid are effective for systemic flares of disease and steroids may be used for significant organ manifestations with or without additional immunosuppressive treatment. Level of evidence III/C; SOA 9.2 (100%).

(ii) Low dose oral prednisolone is effective in treating persistent constitutional symptoms in patients who have failed to respond to HCQ or other immunosuppresants. Level of evidence IIb/B; SOA 8.92 (100%).

Recommended DMARDs

HCQ

Evidence of efficacy of HCQ in SS is variable. A number of studies [144–147] suggest modest improvements in ocular and oral dryness, lowering of ESR and immunoglobulin levels, together with reductions in fatigue levels and joint pain in patients treated with HCQ.

The JOQUER study, a randomized controlled trial of HCQ 400 mg daily, which studied a group with mild disease (i.e. no systemic disease), failed to reach its primary outcome of a 30% improvement in two out of three outcomes (visual analogue scale (VAS) of pain, dryness, fatigue) at 6 months, but it did confirm a decrease in immunoglobulin levels and ESR in treated patients. The study was extended to 48 weeks with all patients being prescribed HCQ between weeks 24 and 48. Although there was a suggestion of clinical and serological improvement in the cohort taking a full 12 months of HCQ, in the open-label extension this did not reach statistical significance [148].

A meta-analysis of six earlier trials involving 140 female patients failed to identify a clear benefit of antimalarials but commented that the available evidence was of poor quality and called for more and better quality research [149].

All members of the guideline working group recommended a therapeutic trial of HCQ treatment in patients with evidence of systemic disease starting at 400 mg once daily decreasing after 6 weeks to 200 mg once daily with monitoring as per BSR guidelines.

Recommendations for HCQ

(i) HCQ up to a maximum dose of 6 mg/kg is recommended for patients with pSS especially those with skin and joint disease and fatigue. Patients should be monitored for evidence of a clinical and/or biological response (e.g. falling immunoglobulin levels). If no response after 12 months of treatment consider stopping. Level of evidence IIa/B; SOA 9.64 (100%).

AZA

AZA has been reported as helpful in case reports for systemic complications such as lung disease [150], myelopathy [151] and cytopaenias [152], but a double blind placebo controlled trial in a small cohort of patients with uncomplicated disease suggested that it did not have a routine role in treatment and was associated with a high frequency of side effects [153]. There is, however, some evidence for efficacy of AZA in both usual interstitial pneumonitis and non-specific interstitial pneumonitis, the most commonly reported forms of ILD in Sjögren's [128, 129, 154, 155]. Discontinuation rates of AZA due to non-respiratory side effects may be higher than for mycophenolate although efficacy is similar in patients with ILD [156].

Recommendations for AZA

(i) AZA is not routinely recommended for management of uncomplicated Sjögren's but may be considered in patients with systemic complications, for example, lung disease, myelopathy and cytopaenias. Level of evidence III/C; SOA 9.09 (100%).

MTX

MTX is the drug of choice for patients with significant inflammatory arthritis [157]. There are case reports of successful treatment of Sjögren's associated inclusion body myositis [158] and myelopathy [159] with MTX. An open label, pilot study of weekly MTX in 17 patients showed improvement in sicca symptoms, parotid swelling, dry cough and purpura but no improvement in objective parameters of dry eyes and mouth [160].

Recommendations for MTX

(i) MTX may be useful for those patients with an associated inflammatory arthritis but there is not enough evidence for its routine use as a disease-modifying drug for those with sicca symptoms alone. Level of evidence IV/D SOA 9.54 (100%).

Mycophenolate

A single centre, open-label pilot trial of mycophenolate in 11 patients reported subjective improvement of ocular dryness and reduction in artificial tear use, but objective evidence of significant glandular improvement in only two patients with short disease duration. There was significant reduction in hypergammaglobulinaemia and RF levels and increase in complements and white cell levels [161]. A case report [162] documents successful treatment of refractory agranulocytosis with mycophenolate in a patient with primary Sjögren's. There is emerging evidence supporting the use of mycophenolate in patients with CTD related ILD including SS [163, 164]. Mycophenolate has been show to stabilize scleroderma associated ILD in a randomized controlled trial [165]. There are to date no similarly robust clinical trials supporting mycophenolate in Sjögren's associated ILD, but there are anecodatal reports and small case series suggesting benefit [166, 167].

Recommendations for mycophenolate

(i) The use of mycophenolate may be considered in patients with systemic complications such as cytopaenias or lung disease. Level of evidence III/C; SOA 9.1 (100%).

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Ciclosporin A

There are anecdotal reports of successful treatment of Sjögren's associated interstitial cystitis [168], annular erythema [169, 170], red cell aplasia [171] and pneumonitis [172] with oral ciclosporin. An open-label phase II study of low dose ciclosporin A (2 mg/kg) showed reductions in joint swelling and tenderness, a fall in the EULAR SS Disease Activity Index and Hospital Anxiety Questionnaire and improvements in both the physical and mental health domains of the Short Form 36 [173].

Recommendations for ciclosporin A

(i) Ciclosporin A is not routinely recommended for management of uncomplicated Sjögren's, although it may be helpful in patients with significant joint involvement. Level of evidence III/C; SOA 8.58 (85.7%).

CYC

There are no controlled trials of CYC in SS and in general its potential toxicity would preclude routine use. However, there are published case reports and series documenting successful treatment of Sjögren's associated myelopathy [133, 138] with pulsed monthly CYC, refractory thrombocytopaenia [174] with pulsed followed by oral CYC, glomerulonephritis [143, 175] with both pulsed and oral CYC and lung disease [176] with pulsed intravenous CYC.

Recommendations for CYC

(i) The use of CYC (usually in combination with steroids) may be considered in patients with organ threatening systemic complications such as CNS, renal or lung disease. Level of evidence III/C; SOA 9.09 (100%).

DMARDs not routinely recommended

LEF

Two phase II open label pilot studies found very modest benefits and multiple side effects [177, 178].

Recommendations for LEF

(i) LEF is not routinely recommended for pSS. Level of evidence III/C; SOA 9.8 (100%).

Penicillamine

A prospective open label study found very modest benefits and multiple side effects [179].

Recommendations for penicillamine

(i) Penicillamine is not routinely recommended for pSS Level of evidence III/C; SOA 10 (100%).

Biologics for systemic disease

Rituximab

There is accumulating evidence from published case studies and case series supporting the use of rituximab in patients with active, systemic pSS.

Rituximab has evidence of efficacy from small case series and case reports in the treatment of Sjögren's related lymphoma, ITP, cryoglobulinaemia and neurological disease [180–190].

A number of open label studies and randomized controlled trials have looked at the effect of rituximab on the fatigue and sicca manifestations (see Supplementary table S3, available at *Rheumatology* online, for a summary). An open label study of 12 patients [191] observed modest improvements in patient reported fatigue and oral dryness at 26 weeks following a single treatment course of rituximab. The TEARS (Tolerance and Efficacy of Rituximab in primary Sjogren's syndrome) study [192] found no significant differences between treatment and placebo arms in the primary end point (an improvement of at least 30 mm in 2 of 4 VAS scores at week 24 following a single treatment course of rituximab). However, there was a significant improvement in the fatigue VAS scores in the treatment group at 6 and 16 weeks. The multicentre UK based TRACTISS (TRial of Anti-B Cell Therapy In patients with primary Sjogren's Syndrome) trial [193] has recently been completed. Although preliminary analysis has shown no consistent benefit on fatigue, dryness and salivary flow, further analysis of data is being conducted. A recent study has suggested that patients with higher levels of B cell infiltration within the parotid glands are more likely to respond to rituximab, suggesting that we may in future be able to target therapy more effectively [194]. There is evidence that B cell activating factor is upregulated after rituximab treatment [195] and this may explain the observation in the TEARS study that patients had improved at 4 months but deteriorated again by 6 months [192].

The dose, duration between doses and treatment response in the smaller studies and case series are listed in Supplementary table S3, available at *Rheumatology* online, but in the TEARS study [192] patients received just two 1 g pulses of rituximab 2 weeks apart at baseline, whereas in the TRACTISS study [193] this was repeated at 6 months.

In conclusion there is currently insufficient evidence to recommend routine use of rituximab in those with predominantly fatigue and sicca manifestations but good evidence for its use in systemic complications and lymphoma. Use of Rituximab in pSS is not currently NICE approved and is not routinely funded for the treatment of SS with the exception of those patients presenting with lymphoma.

Recommendations for rituximab

(i) Rituximab is recommended for specialist use in patients with significant systemic manifestations refractory to treatment with steroids and other immunosuppressives. It has a role in those with lymphoma, ITP, vasculitic neuropathy and cryoglobulinaemias. Level of evidence IIb/B; SOA 9.43 (100%).

Biologics where more evidence of efficacy is required

Belimumab

Belimumab is a human mAb that inhibits B cell activating factor. An open-label study of belimumab, in 30 patients

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with pSS demonstrated a significant improvement in the EULAR SS Disease Activity Index Score from baseline with particular improvement in non-malignant glandular swelling [196]. Although not currently routinely used in Sjögren's syndrome, belimumab has also been reported to be of benefit in case reports in combination with rituximab [197] and further trials of belimumab, including a combined study with rituximab, are currently underway.

Recommendations for belimumab

(i) Belimumab is not currently recommended although it merits further study. Level of evidence IIb/B; SOA 9.46 (92.8%).

Abatacept

Abatacept was well tolerated in one open label pilot study and fatigue and health related quality of life improved significantly over a 24-week treatment period [198]. There is a phase II study currently underway (https://clinicaltrials.gov/ct2/show/NCT02067910).

Recommendations for abatacept

(i) Abatacept is not currently recommended although it merits further study. Level of evidence III/C; SOA 9.46 (92.8%).

Biologics not currently recommended

Anti-TNF therapy

Initial open label studies of anti-TNF agents suggested some benefit [199–201] but subsequent randomized double-blind controlled trials have failed to show clinical or serological improvement in patients with Sjögren's following treatment with anti-TNF in the form of etanercept [201] or infliximab [203].

Recommendations for anti-TNF therapy

(i) Anti-TNF therapies are not recommended for treatment of pSS. Level of evidence Ib/A; SOA 9.38 (85.7%).

IFNα

IFNα therapy via the oro-mucosal route is not currently available in the UK for the treatment of SS, although there is some evidence of efficacy with moderate improvements in unstimulated salivary flow rates in phases II and III studies [204–207].

Recommendations for IFNα

(i) IFNα therapy via the oro-mucosal route is not currently recommended for the treatment of SS. Level of evidence Ib/B; SOA.

Anti-IL1 (anakinra)

A double-blind, placebo-controlled parallel group study [208] of anakinra in pSS failed to reach its primary end point, although more patients on the active drug than on placebo reported a 50% reduction in fatigue.

Recommendations for anti-IL1

(i) Anakinra (an anti-IL-1 receptor antagonist) is not recommended for the treatment of pSS. Level of evidence Ib/A; SOA 9.82 (100%).

Tociluzimab

Tocilizumab, an anti-IL-6 receptor antibody, is used routinely in the treatment of patients with RA but is not licensed for use in SS. A single case report describes successful treatment of refractory organizing pneumonia associated with Sjögren's [209], but there is insufficient evidence to recommend its use pending further studies.

Recommendations for tociluzimab

(i) Tociluzimab (an anti-IL-6 receptor antibody) is not recommended for the treatment of pSS. Level of evidence III/C; SOA 9.82 (100%).

Efalizumab

A small, open label study of three patients showed no clinical improvement and a significant increase in inflammation on minor salivary gland biopsy with the development of new anti-dsDNA antibodies in two of the three subjects [210].

Recommendations for efalizumab

(i) Efalizumab is not recommended for the treatment of pSS. Level of evidence III/C.

Other potential treatments for systemic disease

IVIG

There is evidence supporting the use of immunoglobulin therapy in Sjögren's associated sensorimotor and non-ataxic sensory neuropathy from retrospective and observational cohorts and case reports [211, 212]. Immunoglobulin treatment has also been used successfully in refractory Sjögren's associated myositis not responding to conventional treatment [213]. There is no evidence for its routine use in patients without significant complications.

Recommendations for IVIGs

(i) Immunoglobulin treatment is not routinely used in pSS, although it may be effective in Sjögren's associated myositis and neuropathies and its use in these conditions may be justified if the patient has failed to respond to treatment with steroids and conventional immunosuppression. Level of evidence III/C; SOA 9.43 (100%).

Colchicine

There are case reports describing successful treatment of Sjögren's associated hypergammaglobulinaemic purpura [214], granulomatous panniculitis [215] and pericarditis [216] with colchicine.

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Recommendations for colchicine

(i) Colchicine may be considered as adjunctive treatment in patients with cutaneous manifestations or pericarditis not responding to HCQ or other treatments. Level of evidence III/C; SOA 8.45 (85.7%).

Dapsone

There are case reports describing successful treatment of Sjögren's associated scLE and urticarial vasculitis [217], pyoderma gangrenosum [218] and cutaneous vasculitis [219] with dapsone.

Recommendations for dapsone

(i) Dapsone may be considered as adjunctive treatment in patients with cutaneous manifestations not responding to HCQ. Level of evidence III/C; SOA 8.8 (100%).

Topical tacrolimus

There are case reports describing successful treatment of annular erythema associated with SS [220] with topical tacrolimus. Studies of tacrolimus suggest an increased incidence of skin cancer, so it should be used sparingly for a limited amount of time.

Recommendations for tacrolimus

(i) Topical tacrolimus may be considered as adjunctive treatment in patients with cutaneous manifestations not responding to HCQ. Level of evidence III/C; SOA 8.75 (100%).

Other drugs not recommended

Dehydroepiandrosterone substitution treatment

Two double-blinded, randomized studies of DHEA treatment in SS failed to show any symptomatic improvement or changes in clinical or serological measures in treated patients compared with placebo [221, 222].

Recommendations for DHEA

(i) DHEA substitution treatment is not recommended in pSS. Level of evidence Ib/A; SOA 9.45 (100%).

Management of pregnancy

Fertility is normal in patients with pSS, although there is an increased risk of recurrent miscarriage in the Ro/La$^+$ group [223–225]. Neonatal lupus rash occurs in about 5% of live births in Ro/La positive women usually appearing at 6 weeks of age and lasting about 17 weeks before fading and clearing completely. A few children have persistent depigmentation or telangiectasia [226]. Congenital heart block occurs in $<2\%$ of pregnancies in women with anti-Ro or anti-La antibodies and may be detected by US scanning from about 16 weeks' gestation [227]. There is evidence that in anti-Ro positive women, fetal atrioventricular (AV) time intervals are longer and heart rates slightly lower compared with controls. Fetuses with normal AV time intervals at 18–24 weeks had normal electrocardiographic results at birth. Hence serial Doppler echocardiographic measurement of AV time intervals is suggested as a useful method for surveillance of these high-risk pregnancies [228]. Following an affected pregnancy the risk of congenital heart block goes up to 17% for subsequent pregnancies. Seventy per cent of affected children survive, but nearly all require pacemakers in the first few months of life [229]. There is some evidence from longitudinal, observational studies that primary SS mothers deliver significantly earlier, give birth to babies with lower birth weight and have complications during deliveries more frequently than women in the general population [227]. Other, very rare, complications include hepatitis and cytopenias affecting the newborn. Only a handful of cases have been reported in the literature and in the majority of cases the child has improved spontaneously [230].

Successful pregnancies are, however, increasingly common in patients with Sjögren's. There is evidence that low-dose aspirin initiated in early pregnancy improves placental implantation and reduces the incidence of both pre-eclampsia and intra-uterine growth retardation [231, 232]. The working group therefore recommended that in Sjögren's pregnancy one should consider low dose aspirin to improve placental implantation and monitor closely with serial US. It is safe to continue HCQ throughout pregnancy with evidence in patients with SLE of improved outcomes for the mother and no detrimental effects on the child [233–236]. Refer to the BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding [235, 236].

Recommendations for management of pregnancy

(i) Consider low dose aspirin to improve placental implantation. Level of evidence IIb/B; SOA 8.27 (92.8%).
(ii) Monitor closely with serial US if anti-Ro and/or anti-La positive and consider referral to specialist centre. Level of evidence IIb/B; SOA 9.71 (100%).
(iii) Review all medication in pregnancy. HCQ may be continued throughout pregnancy and breastfeeding. Level of evidence I/A; SOA 7.91 (85.7%).

Assessment of lymphoma risk

The risk of lymphoma development in patients with primary SS increases from 3% in the first 5 years to 9.8% at 15 years, that is, up to 40 times the population risk [237–239]. The presence of lymphadenopathy, parotid enlargement, palpable purpura, low serum C4 levels and cryoglobulins are the most consistent predictors of future risk [240] and may increase the risk of future development of lymphoma up to 5-fold [238]. The detection of germinal centre-like structures or a focus score $\geqslant 3$ on light microscopy in diagnostic salivary gland biopsies from patients with pSS may suggest a future higher risk for lymphoma development [241]. The majority of lymphomas are of the mucosa-associated lymphoid tissue type. The median age of onset is mid-50s and the diagnosis of Sjögren's generally predates the lymphoma by a mean of 7 years [237].

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Commonest sites of presentation include the parotid and other salivary glands, followed by the orbits, stomach, thyroid, lung, upper airways and rarely other sites [242]. Presentation is usually with a firm, palpable swelling within the gland. GI tract lymphoma may present with chronic diarrhoea, malabsorption and weight loss [243].

Recommendations for assessment of lymphoma risk

(i) Review high risk patients regularly and warn patients to report firm, painless glandular swelling that does not settle. Level of evidence IV/D; SOA 9.86 (100%).

Management of lymphoma

US allows assessment of any new swelling within the major salivary glands and, used in conjunction with Doppler signals, may help differentiate between benign and malignant lesions [111].

Biopsy is usually necessary to confirm the diagnosis. CT scanning is helpful for staging. Treatment can be variable and may include a watch and wait approach in patients with localized low-grade lymphoma or radiation alone but is generally with surgical excision followed by radiotherapy, chemotherapy, generally including rituximab, or a combination of the two. There are regularly updated UK guidelines available. The prognosis is generally good with a complete response to initial treatment in >90% and 5-year disease-free survival >75% [242], but splenomegaly, low serum C3, levels, neutropenia and lymphopenia may indicate a higher risk of poor outcome [240]. Refer to Haematology/Oncology for detailed advice on management.

Recommendations for management of lymphoma

(i) Investigate suspicious lesions with local US, biopsy and CT chest, abdomen and pelvis for staging. Level of evidence III/C; SOA9.77 (100%).

Conclusion

pSS is a chronic, debilitating condition that warrants effective management. All patients should be counselled and offered topical management for sicca symptoms. Systemic treatment should be considered early in those with constitutional symptoms.

Applicability and utility

Key standards of care and potential organizational barriers to implementation

pSS is associated with significant direct and indirect costs and represents a significant impact on the healthcare system [244, 245]. The initial management of SS includes educating the patient on appropriate management and initiating simple treatments such as moisturizing eye drops and fluorinated mouth gels. This is best done by a physician with an interest and some background knowledge. Patients also benefit from the additional time and expertise of an appropriately trained specialist nurse. A baseline ophthalmic and oral medicine specialist assessment are recommended. Appropriate early management will improve outcomes for patients and prevent the development of excess dental caries and potentially reduce the future health care needs of these patients. A multi-disciplinary clinic setting has been shown by one specialist unit to provide a cost effective and high quality environment for patient care while facilitating involvement in research [246].

Mechanism for audit of the guideline

An audit pro forma to assess compliance with these guidelines is available on the BSR website.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: B.A.F. has received honoraria from Novartis and Medimmune. W.-F.N. has provided scientific consultancy for Takeda, MedImmune, UCB, Sanofi, Eli-Lily, AbbVie and have received research support from Resolve Therapeutics. S.B. has consulted for a number of Pharmaceutical Companies in the field of clinical trial design Sjogren's Syndrome (AstraZeneca/Medimmune, BMS, Celgene, Eli Lilly, Glenmark, GSK, MTPharma, Novartis, Ono, Pfizer, Takeda, UCB, xtlbio). F.B. works in a unit that has received funding from GSK and USB. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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Systemic sclerosis

FAIK NOORI

ACR/EULAR Classification Criteria for Systemic Sclerosis (SSc, Scleroderma)

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Disclosure

- This project was jointly funded by
  - American College of Rheumatology (ACR)
  - European League Against Rheumatism (EULAR)

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Objectives

1. To understand the strengths and weaknesses of the current classification criteria in SSc
2. To become familiar with how to use the new criteria in SSc

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ARTHRITIS & RHEUMATISM
Vol. ●, No. ●, ● 2013, pp xx–xx
DOI 10.1002/art.●
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Arthritis & Rheumatism
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SPECIAL ARTICLE

AQ: 1

2013 Classification Criteria for Systemic Sclerosis

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

Frank van den Hoogen,[1] Dinesh Khanna,[2] Jaap Fransen,[3] Sindhu R. Johnson,[4] Murray Baron,[5] Alan Tyndall,[6] Marco Matucci-Cerinic,[7] Raymond P. Naden,[8] Thomas A. Medsger Jr.,[9] Patricia E. Carreira,[10] Gabriela Riemekasten,[11] Philip J. Clements,[12] Christopher P. Denton,[13] Oliver Distler,[14] Yannick Allanore,[15] Daniel E. Furst,[12] Armando Gabrielli,[16] Maureen D. Mayes,[17] Jacob M. van Laar,[18] James R. Seibold,[19] Laszlo Czirjak,[20] Virginia D. Steen,[21] Murat Inanc,[22] Otylia Kowal-Bielecka,[23] Ulf Müller-Ladner,[24] Gabriele Valentini,[25] Douglas J. Veale,[26] Madelon C. Vonk,[3] Ulrich A. Walker,[6] Lorinda Chung,[27] David H. Collier,[28] Mary Ellen Csuka,[29] Barri J. Fessler,[30] Serena Guiducci,[7] Ariane Herrick,[31] Vivien M. Hsu,[32] Sergio Jimenez,[33] Bashar Kahaleh,[34] Peter A. Merkel,[35] Stanislav Sierakowski,[23] Richard M. Silver,[36] Robert W. Simms,[35] John Varga,[37] and Janet E. Pope[38]

This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an external data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

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ARTHRITIS & RHEUMATISM
Vol. ●, No. ●, ● 2013, pp xx–xx
DOI 10.1002/art.●
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Arthritis & Rheumatism
An Official Journal of the American College of Rheumatology
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SPECIAL ARTICLE

AQ: 1

2013 Classification Criteria for Systemic Sclerosis

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Robert

This criteria set has been approved
European League Against Rheuma
been quantitatively validated using
All ACR/EULAR-approved criteria

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Criteria

2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative

Frank van den Hoogen,[1] Dinesh Khanna,[2] Jaap Fransen,[3] Sindhu R Johnson,[4] Murray Baron,[5] Alan Tyndall,[6] Marco Matucci-Cerinic,[7] Raymond P Naden,[8] Thomas A Medsger Jr,[9] Patricia E Carreira,[10] Gabriela Riemekasten,[11] Philip J Clements,[12] Christopher P Denton,[13] Oliver Distler,[14] Yannick Allanore,[15] Daniel E Furst,[12] Armando Gabrielli,[16] Maureen D Mayes,[17] Jacob M van Laar,[18] James R Seibold,[19] Laszlo Czirjak,[20] Virginia D Steen,[21] Murat Inanc,[22] Otylia Kowal-Bielecka,[23] Ulf Müller-Ladner,[24] Gabriele Valentini,[25] Douglas J Veale,[26] Madelon C Vonk,[3] Ulrich A Walker,[6] Lorinda Chung,[27] David H Collier,[28,29] Mary Ellen Csuka,[30] Barri J Fessler,[31] Serena Guiducci,[7] Ariane Herrick,[32,33] Vivien M Hsu,[34] Sergio Jimenez,[35] Bashar Kahaleh,[36] Peter A Merkel,[37,38] Stanislav Sierakowski,[23] Richard M Silver,[39] Robert W Simms,[38] John Varga,[40] Janet E Pope[41]

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SSc Criteria were developed collaboratively

Frank van den Hoogen, Dinesh Khanna, Jaap Fransen, Sindhu R. Johnson, Murray Baron, Alan Tyndall, Marco Matucci-Cerinic, Raymond Naden, Thomas A Medsger Jr., Patricia Carreira, Gabriela Riemekasten, Phillip Clements, Christopher P Denton, Oliver Distler, Yannick Allanore, Daniel E Furst, Armando Gabrielli, Maureen Mayes, Jacob M van Laar, James R Seibold, Laszlo Czirjak, Virginia Steen, Murat Inanc, Otylia Kowal-Bielecka, Ulf Müller-Ladner Gabriele Valentini, Douglas Veale, Madelon Vonk, Ulrich A Walker, Lorinda Chung, Dave Collier, Mary Ellen Csuka, Barry J Fessler, Serena Guiducci, Ariane Herrick, Vivian Hsu, Sergio Jimenez, Bashar Kahaleh, Peter Merkel, Stanislav Sierakowski, Richard Silver, Rob Simms, John Varga, Janet E Pope

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Why do we need SSc classification criteria?

1. To enroll SSc patients in studies (i.e., meeting classification criteria)
2. To differentiate SSc from other mimickers
3. To help to understand pathophysiology, subsets of patients with various features

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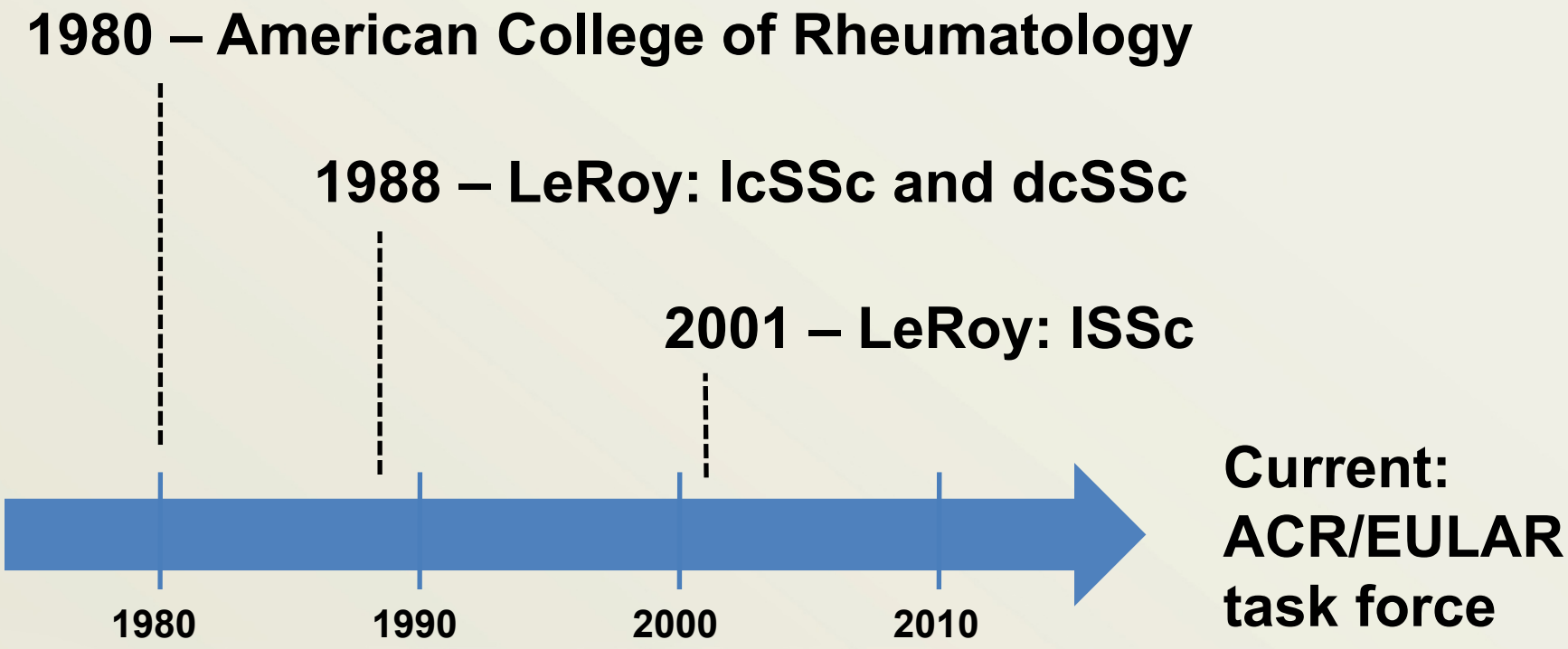
Classification schemes – Overview



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Which patient(s) meet the 1980 ACR SSc classification criteria?

1. Sclerodactyly, Raynaud's, positive anti-centromere, pulmonary arterial hypertension
2. Sclerodactyly, GERD, dilated esophagus, dysphagia RNA polymerase III, Scleroderma renal crisis
3. Sclerodactyly, Raynaud's, anti-centromere, dysphagia, dilated nailfold capillaries, calcinosis
4. Modified Rodnan skin score of 20 including finger involvement
5. Modified Rodnan skin score of 20 and no finger involvement ever, no Raynaud's Phenomenon and negative ANA

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23:581-90

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Which patient(s) meet the 1980 ACR SSc classification criteria?

1. Sclerodactyly, Raynaud's, positive anti-centromere, pulmonary arterial hypertension **NO**
2. Sclerodactyly, GERD, dilated esophagus, dysphagia RNA polymerase III, Scleroderma renal crisis **NO**
3. Sclerodactyly, Raynaud's, anti-centromere, dysphagia, dilated nailfold capillaries, calcinosis **NO**
4. Modified Rodnan skin score of 20 including finger involvement
5. Modified Rodnan skin score of 20 and no finger involvement ever, no Raynaud's Phenomenon and negative ANA **NO**

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23:581-90

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1980 ACR Scleroderma Classification Criteria

- **Major criterion:** proximal cutaneous sclerosis/skin thickening (non-pitting) proximal to the MCPs (metacarpophalangeal joints), affecting other parts of the body
  - usually bilateral, symmetrical, and almost always including sclerodactyly
  - **The major criterion is sufficient.**
- **Minor criteria: 2 or 3 are needed if no major criterion:**
  - sclerodactyly
  - digital pitting scars of fingertips or loss of substance of the distal finger pad
  - bibasalar pulmonary fibrosis

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1 major criterion or ≥ 2 minor criteria were found in 97% of definite SSc cases (sensitivity 97%) but in only 2% of the comparison patients (specificity 98%)

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23:581-90.

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What are the limitations of the 1980 ACR classification criteria for SSc?

1. They don't classify some of those with limited cutaneous SSc
2. They don't always classify early SSc
3. They don't include antibodies that are common in SSc such as anti-centromere
4. They don't include nailfold changes that could help differentiate SSc from primary Raynaud's Phenomenon (RP)

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23:581-90

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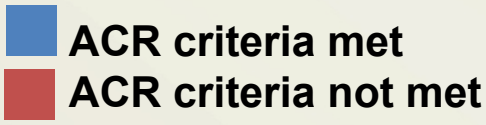
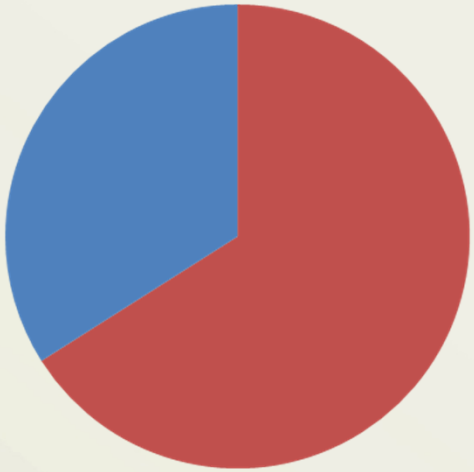
Limitations of the 1980 ACR Scleroderma classification

- Pittsburgh cohort of 639 patients with SSc[1]
  - 20% of limited SSc patients did not meet ACR criteria



- French Canadian cohort of 259 patients with SSc[2]
  - 66% of limited SSc patients did not meet ACR criteria



- **10 to 20% of limited SSc patients do not meet criteria for SSc[3]**
- Many SSc patients diagnosed by expert clinicians would be excluded based on ACR criteria

1. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23:581-90 2. Lonzetti LS, *et al*. *Arthritis Rheum* 2001; 44:735-6. 3. J Walker, J Pope Clinical Rheumatol 2007

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Development of Classification and Response Criteria for Rheumatic Diseases

CLASSIFICATION AND RESPONSE CRITERIA SUBCOMMITTEE OF THE AMERICAN COLLEGE OF RHEUMATOLOGY COMMITTEE ON QUALITY MEASURES

Collaboration between experts and clinical epidemiologists

Balance of expert based and data driven methods

Avoid circularity of reasoning

Evaluate psychometric properties of candidate criteria

Singh JA, et al. Arthritis Rheum. 2006 Jun 15;55(3):348-52.

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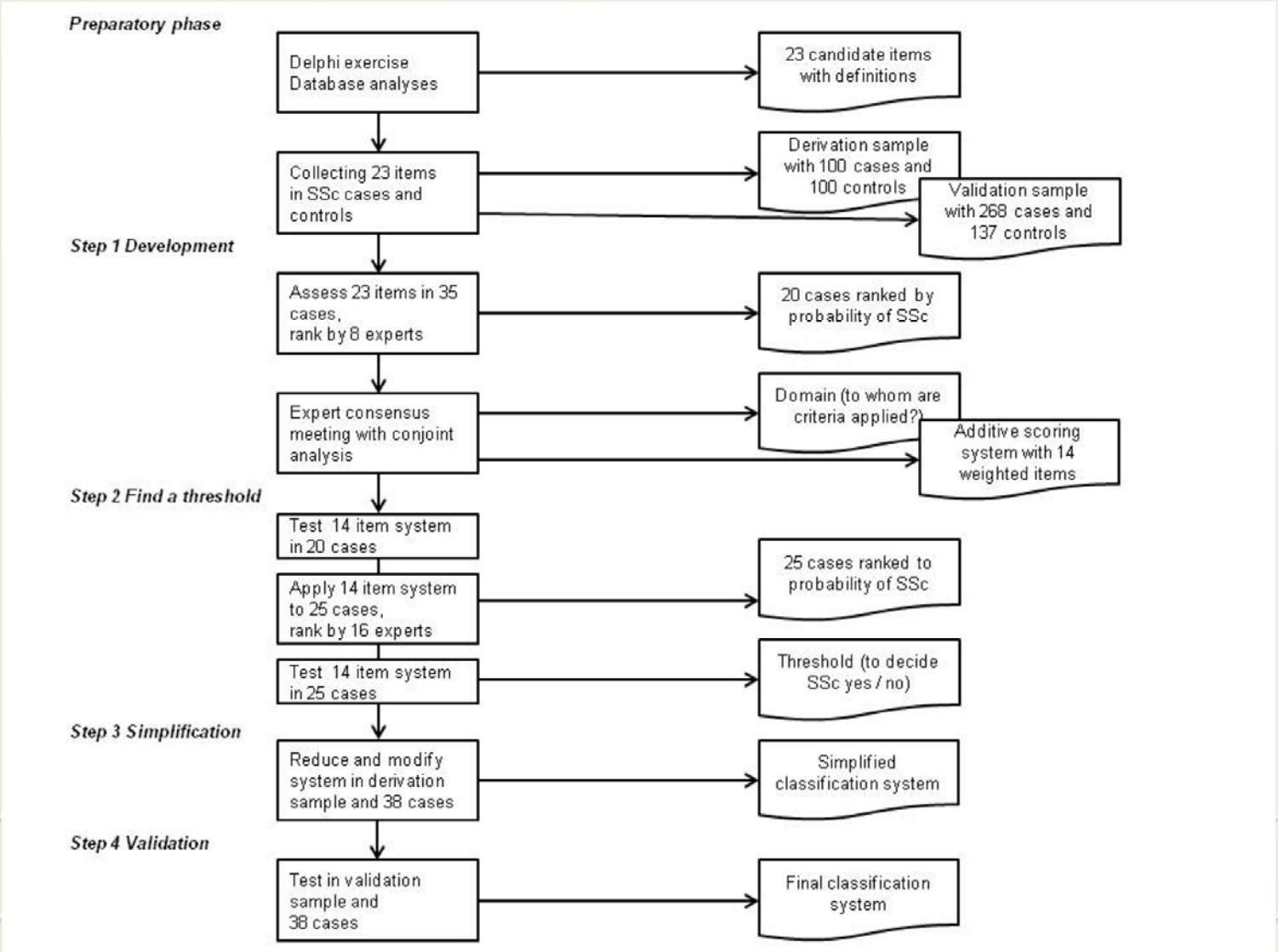
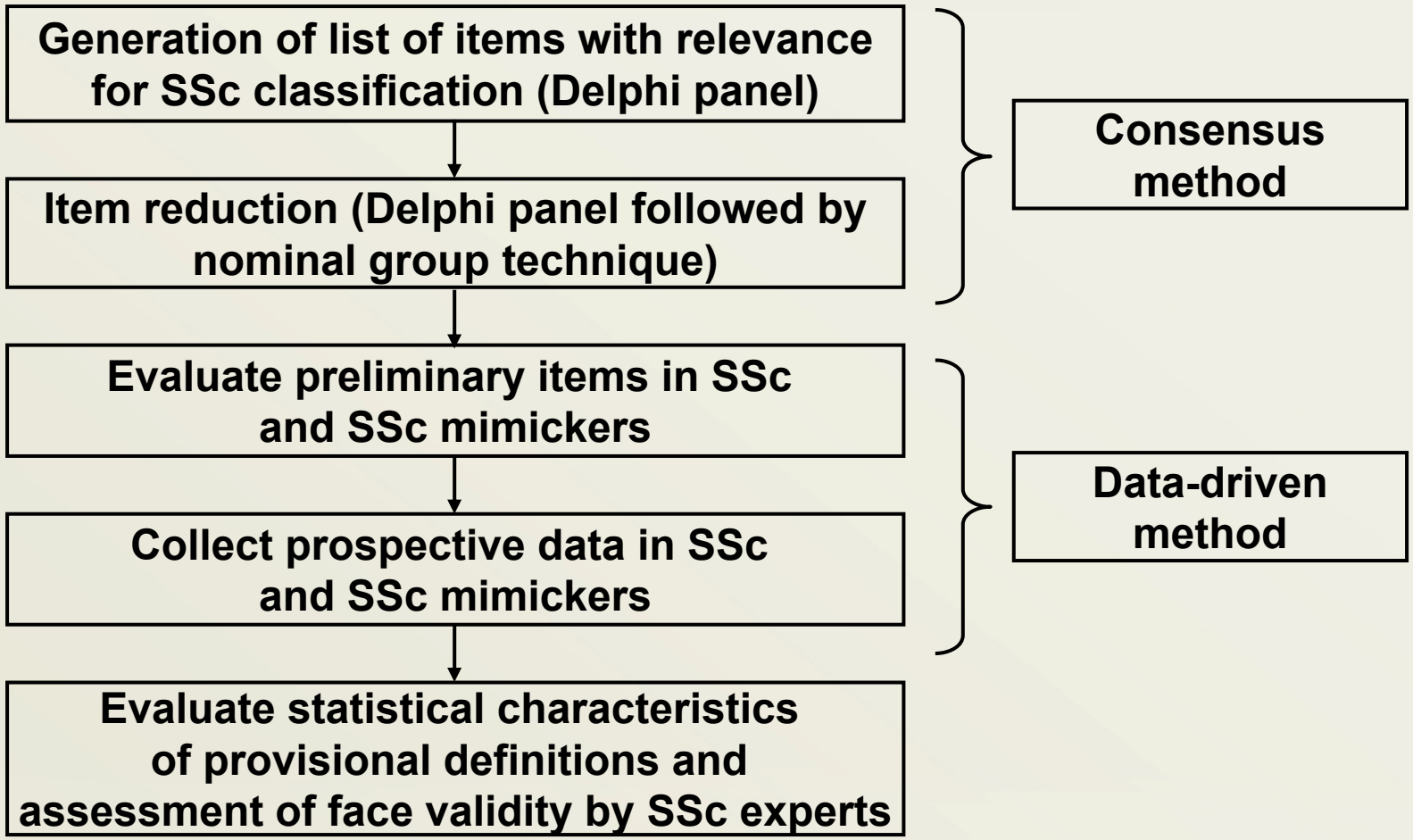
Overview of the ACR / EULAR SSc Classification Criteria Development


Preparatory phase
Delphi exercise
Database analyses
23 candidate items with definitions
Collecting 23 items in SSc cases and controls
Derivation sample with 100 cases and 100 controls
Validation sample with 268 cases and 137 controls
Step 1 Development
Assess 23 items in 35 cases, rank by 8 experts
20 cases ranked by probability of SSc
Expert consensus meeting with conjoint analysis
Domain (to whom are criteria applied?)
Additive scoring system with 14 weighted items
Step 2 Find a threshold
Test 14 item system in 20 cases
Apply 14 item system to 25 cases, rank by 16 experts
25 cases ranked to probability of SSc
Test 14 item system in 25 cases
Threshold (to decide SSc yes / no)
Step 3 Simplification
Reduce and modify system in derivation sample and 38 cases
Simplified classification system
Step 4 Validation
Test in validation sample and 38 cases
Final classification system

Reclassification of SSc by the ACR / EULAR Task Force


Generation of list of items with relevance for SSc classification (Delphi panel)
Item reduction (Delphi panel followed by nominal group technique)
Evaluate preliminary items in SSc and SSc mimickers
Collect prospective data in SSc and SSc mimickers
Evaluate statistical characteristics of provisional definitions and assessment of face validity by SSc experts
Consensus method
Data-driven method

SSc mimickers = eosinophilic fasciitis, generalised morphea, other connective tissue disease, scleromyxedema, etc.

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Delphi results: Items to be tested for the new ACR / EULAR SSc criteria

Item	Appropriateness score* (median)	TOP score	Rank
Positive antitopoisomerase I	9	73%	1
Presence of scleroderma	9	70%	2
Abnormal nailfold capillary pattern	9	67%	3
Positive anticentromere	9	62%	4
Positive anti-RNA polymerase III	8	43%	5
Finger tip ulcers or pitting scars	8	34%	6
Raynaud's phenomenon	7	33%	7
Interstitial lung disease/pulmonary fibrosis	7	28%	8
Renal crisis	8	27%	9

*Scored from 1 to 9, with a higher score denoting greater appropriateness for the classification of SSc

Fransen J, et al. Arthritis Care Res (Hoboken). 2012 Mar;64(3):351-7.

DATA driven validation of top SSc items for criteria from DELPHI exercise

Criterion	Pooled mean OR (95% CrI)	Empiric ranking	Expert based ranking
Renal crisis	NC	1[ab]	9
Digital pulp loss or acro-osteolysis	NC	1[ab]	13[b]
Scleroderma	426.7 (256.5, 691.2)	2	1
Telangiectasia	91.4 (57.6, 154.5)	3	11
Anti-RNA polymerase III antibody	75.4 (13.2, 312.6)	4	6
Puffy fingers	34.9 (24.0, 49.2)	5	12
Finger or wrist flexion contracture	29.0 (17.8, 46.2)	6	19
Tendon or bursal friction rubs	26.81 (2.4, 91.9)	7	10
Anti-topoisomerase-1 antibody	24.9 (12.7, 48.0)	8	2
Raynaud's phenomenon	24.1 (15.3, 37.5)	9	7
Finger tip ulcers or pitting scars	19.3 (12.7, 28.8)	10	5
Anti-centromere antibody	13.8 (9.0, 21.0)	11	3
Abnormal nailfold capillary pattern	10.4 (6.9, 15.1)	12	4
Gastro-esophageal reflux disease	7.8 (6.1, 10.0)	13	17
Antinuclear antibody	6.06 (4.1, 8.8)	14	13[b]
Calcinosis	6.05 (3.4, 10.5)	15	18
Dysphagia	5.7 (4.2, 7.7)	16	19
Esophageal dilatation	5.6 (2.9, 10.2)	17	14
Interstitial lung disease	4.5 (3.4, 5.8)	18	8
Anti-PM-SCL antibody	2.4 (1.9, 7.1)	19	20[b]
Pulmonary arterial hypertension	1.2 (0.9, 1.5)	20	15
Carbon monoxide diffusion capacity (DLCO)	1.5 (1.1, 2.0)	21	16
Forced vital capacity (FVC)	0.9 (0.6, 1.3)	22	20[b]

NC= Not Calculable

Johnson SR, et al. Arthritis Care Res (Hoboken). 2012 Mar;64(3):358-67.

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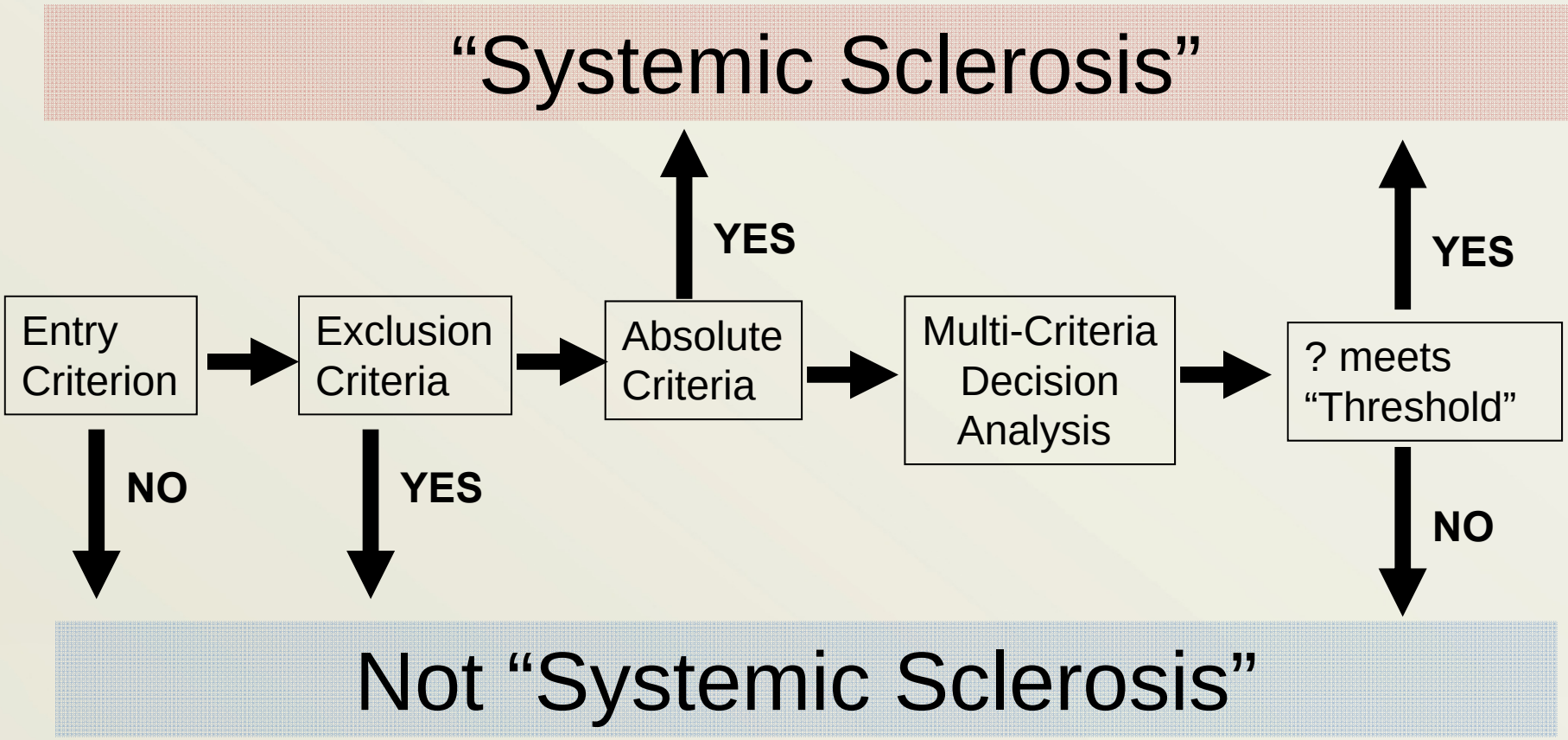
Classification of "Systemic Sclerosis"
ACR / EULAR



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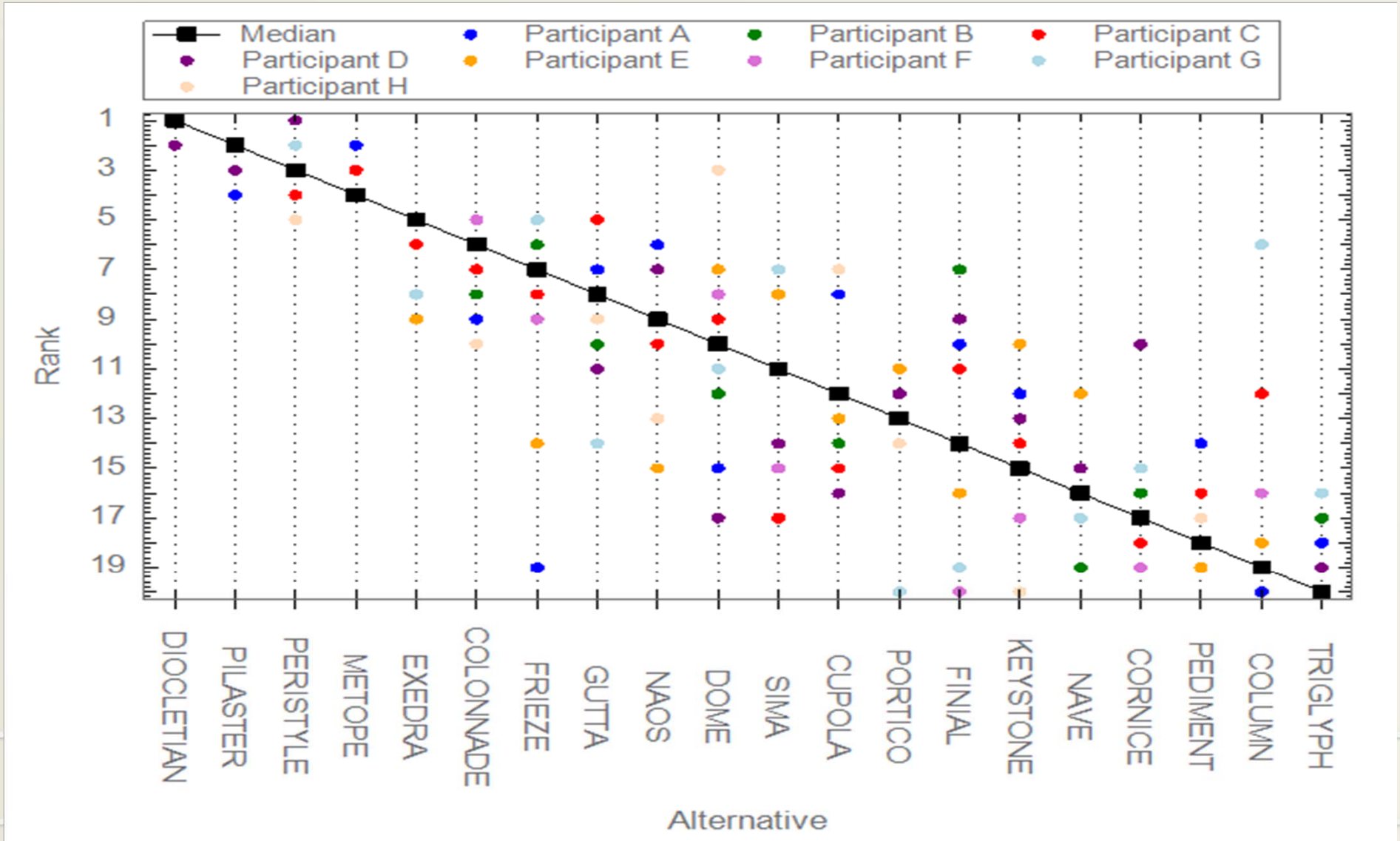
Ranking of cases with a spectrum of probabilities as having SSc



Item	Derivation sample			Validation sample		
	SSc	Scleroderma-like disorder	p-value	SSc	Scleroderma-like disorder	p-value
N=	100	100	--	268	137	--
Age	55 (13)	51 (15)	0.05	54 (13)	52 (15)	0.17
Female	86 (86%)	79 (79%)	0.25	221 (83%)	101 (75%)	0.08
Region						
North America	50	50	--	191 (68%)	91 (32%)	
Europe	50	50		77 (63%)	46 (37%)	0.32
Time since onset of Raynaud's (years)	13 (7-18)	12 (4-18)	0.42	9 (5-18)	10 (4-22)	.40
Time since first non-Raynaud's symptom (years)	10 (4-13)	9 (2-14)	0.58	7 (3-12)	7 (3-15)	.89
Time since diagnosis (years)	8 (3-12)	6 (1-9)	0.10	5 (2-11)	4 (1-7)	.016
Scleroderma-like disorders		28 (28%)			32 (23%)	
systemic lupus erythematosus						
polymyositis/ dermatomyositis		23 (23%)			21 (15%)	
primary Raynaud's syndrome		19 (19%)			7 (5%)	
mixed connective tissue disease		9 (9%)			14 (10%)	
undifferentiated connective tissue disease		8 (8%)			17 (12%)	
eosinophilic fasciitis		6 (6%)			16 (12%)	
nephrogenic sclerosing fibrosis		3 (3%)			3 (2%)	
generalized morphea		5 (5%)			8 (6%)	
scleromyxedema		1 (1%)			3 (2%)	
graft versus host disease		3 (3%)			3 (2%)	
other diagnoses		8 (8%)			13 (9%)	
Manifestations						
Raynaud's phenomenon	91 (91%)	49 (49%)	<0.0001	257 (96%)	63 (46%)	<0.0001
Autoantibodies	68	7 (7%)	<0.0001	137	15 (11%)	<0.0001

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1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sensitivity and Specificity on ACR-EULAR Classification Criteria for SSc

	Derivation sample (N=200)		Validation sample (N=405)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
1980 ARA SSc Criteria	.80 (.72-.87)	.77 (.68-.84)	.75 (.70-.80)	.72 (.64-.79)
2001 LeRoy and Medsger criteria	.76 (.68-.84)	.69 (.68-.84)	.75 (.70-.80)	.78 (.70-.85)
2013 SSc Criteria	.95 (.90-.98)	.93 (.86-.97)	.91 (.87-.94)	.92 (.86-.96)

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Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits - a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other reasons such as inflammatory dactylitis.
Finger tip ulcers or pitting scars	Ulcers or scars distal to or at the PIP joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischemia, rather than trauma or exogenous causes.
Telangiectasia	Telangiectasia(e) in a scleroderma like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or large matt-like telangiectasia(e). Telangiectasiae are visible macular dilated superficial blood vessels; which collapse upon pressure and fill slowly when pressure is released; distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with SSc	Enlarged capillaries and/or capillary loss with or without peri-capillary hemorrhages at the nailfold and may be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right heart catheterization according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis on HRCT or chest radiograph, most pronounced in the basilar portions of the lungs, or presence of 'Velcro' crackles on auscultation not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self report or reported by a physician with at least a two-phase color change in finger(s) and often toe(s) consisting of pallor, cyanosis and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
Scleroderma specific antibodies	Anti-centromere antibody or centromere pattern on antinuclear antibody (ANA) testing; anti-topoisomerase I antibody (also known as anti-Scl70 antibody); or anti-RNA polymerase III antibody. Positive according to local laboratory standards.

Defini-tions of terms

Classification criteria

- They are not diagnostic criteria but hopefully are close
- Thus early patients may not be classified
- Classification criteria do not equal diagnositic criteria, so it is possible that some patients may be diagnosed with SSc but don't meet the ACR / EULAR SSc classification criteria

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Use of the ACR / EULAR SSc classification criteria

- **Exclusion criteria**
  - You know there is a different disease
  - Absence of sclerodactyly (ever) if skin involvement is elsewhere
- **Absolute inclusion criterion**
  - Scleroderma skin involvement with sclerodactyly and contiguous skin involvement proximal to the MCPs

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Caveats for ACR / EULAR SSc classification criteria

- Mark highest score in each category
- Not all centers have access to RNApolymerase III Ab
- Don’t apply criteria if you don’t think patient has SSc or have a better explanation
  - Such as generalized morphea
- You can have more than one connective tissue disease (CTD) so a patient can have an overlap with SSc as one of the diseases and some patients with mixed connective tissue disease may be classified with SSc

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Conclusions

- There is a need to effectively classify SSc patients
- Classification systems have evolved over the years with advancing technology
  - Capillaroscopy, autoantibodies, new methodologies
- Patients can be classified with more than one disease with the ACR / EULAR SSc classification criteria (i.e., overlaps)
- You have to do some math!
- Current classification includes more patients who would not have been classified by previous criteria

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Conclusions about 2013 ACR/EULAR SSc classification criteria

- Items have good face validity
- Items have good discriminant validity
- Items have good construct validity
- The sensitivity and specificity of the ACR/EULAR SSc classification criteria are better than previous criteria

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Using the 2013 ACR / EULAR SSC Classification Criteria

- Apply the criteria for SSc, if appropriate

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1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly,
Raynaud's,
+ anti-centromere,
pulmonary arterial hypertension

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1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly 4, Raynaud's 2, + anti-centromere 3, pulmonary arterial hypertension, ILD 2

Score 11

Yes, criteria are met

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Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly, GERD, dilated esophagus, dysphagia RNA polymerase III, Scleroderma renal crisis

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly, 4
GERD, 0
dilated esophagus,0
dysphagia 0
RNA polymerase III 3,
Scleroderma renal crisis 0

Total score 7, SSc criteria not met

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
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	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly just to PIP,
GERD, dilated esophagus, dysphagia
RNA polymerase III, RNP+
Scleroderma renal crisis

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Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly just to PIP, 0
GERD 0, dilated esophagus 0, dysphagia 0
RNA polymerase III 3,
RNP+ 0
Scleroderma renal crisis 0

Total 3

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly, Raynaud's, + anti-centromere, dysphagia, dilated nailfold capillaries, calcinosis

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly 4, Raynaud's 3, + anti-centromere 3, Dysphagia 0, dilated nailfold capillaries 2, calcinosis 0

Total score 12

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions *(only count the highest score)*	Digital Tip Ulcers	2
	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Modified Rodnan skin score of 20 including finger involvement
Raynaud's
ANA
nucleolar
GERD
ILD

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Modified Rodnan skin score of 20 including finger involvement 9
Raynaud's 3
ANA nucleolar 0
GERD 0
ILD 2

Total score 14

NB criterion is met for skin thickening proximal to MCP so criteria don't need to be applied

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
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Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Modified Rodnan skin score of 20 and no finger involvement ever

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions *(only count the highest score)*	Digital Tip Ulcers	2
	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Modified Rodnan skin score of 20 and no finger involvement ever

Don't apply the criteria N/A Skin thickening sparing the fingers are not cl

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

No skin involvement ever, Telangiectasia, PAH, Raynaud's, +ANA

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

No skin involvement ever 0, Telangiectasia 2, PAH 2, Raynaud's 3, +ANA 0

Total score 7

SSc Criteria are not currently met

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

No skin involvement ever, Telangiectasia, PAH, Raynaud's, +ANA, +anti-centromere Ab

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

No skin involvement ever 0, Telangiectasia 2, PAH 2, Raynaud's 3, +ANA 0, +anti-centromere Ab 3

Total score 10

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

No skin involvement ever, Telangiectasia, ILD, PAH, Raynaud's, +ANA +Scl70 (topo1)

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

No skin involvement ever 0, Telangiectasia 2, ILD and PAH 2, Raynaud's 3, +ANA 0, +Scl70 (topo1) 3

Total score 10

Not PAH and/or ILD count total of 2

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1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

No skin involvement ever, Telangiectasia, PAH, Raynaud's, +ANA, dilated capillaries at nailbeds in past (well documented)

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

No skin involvement ever, 0
Telangiectasia, 2
PAH, 2
Raynaud's, 3
+ANA, 0
dilated capillaries at nailbeds in past (well documented) 2

Total score 9
Criteria are met

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
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Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers, Raynaud's, Abnormal nailfold cap, +ANA
New dysphagia retrosternally, Scleroderma renal crisis

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers, 2
Raynaud's, 3
Abnormal nailfold cap, 2
+ANA 0
New dysphagia retrosternally, 0
Scleroderma renal crisis 0

Total score 7
Criteria are not met

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers, Raynaud's, Abnormal nailfold cap, +ANA
New dysphagia retrosternally, Scleroderma renal crisis, tendon friction rubs

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers, 2
Raynaud's, 3
Abnormal nailfold cap, 2
+ANA 0
New dysphagia retrosternally, 0
Scleroderma renal crisis, 0
tendon friction rubs 0

Total score 7
Criteria are not met

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers, Raynaud's, Abnormal nailfold cap, +ANA 0
New dysphagia retrosternally, 0
Scleroderma renal crisis, 0
+RNApol III

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers, 2
Raynaud's, 3
Abnormal nailfold cap, 2
+ANA 0
New dysphagia retrosternally, 0
Scleroderma renal crisis, 0
+RNApol III 3

Total score 10

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers, Raynaud's, Abnormal nailfold cap, +ANA New dysphagia retrosternally, Scleroderma renal crisis, +RNApol III, tendon friction rubs, Digital ulcers

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers, 2
Raynaud's, 3
Abnormal nailfold cap, 2
+ANA 0
New dysphagia retrosternally, 0
Scleroderma renal crisis, 0
+RNApol III, 3
tendon friction rubs, 0
Digital ulcers 2

Total score 12

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly dital to PIPs, Raynaud's, Abnormal nailfold cap in past, +ANA with anti-centromere pattern, Digital pitted scars

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly dital to PIPs, 0 Raynaud's, 3 Abnormal nailfold cap in past, 2 +ANA with anti-centromere pattern, 3 Digital pitted scars 3

Total score 11

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly dital to PIPs, Raynaud's, +ANA with anti-centromere Telangiectasia, calcinosis

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly dital to PIPs, 0 Raynaud's, 3 +ANA with anti-centromere 3 Telangiectasia, 2 calcinosis 0

Total score 8 SSc criteria not met

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly whole fingers and tight mouth and face, Raynaud's, +ANA with anti-centromere Telangiectasia, calcinosis

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly whole fingers and tight mouth and face, 4 Raynaud's, 3 +ANA with anti-centromere 3 Telangiectasia, 2 calcinosis 0

Total score 12

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly whole fingers and continous proximal to MCPs to hand, Raynaud's, +ANA Telangiectasia, calcinosis Needing repeat esophageal dilations

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sclerodactyly whole fingers and continous proximal to MCPs to hand, 9
Raynaud's, 3
+ANA 0
Telangiectasia,2
calcinosis 0
Needing repeat esophageal dilations 0

Total score 14

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Tight skin but sparing fingers and hands,
Monoclonal gammapathy,
neg ANA,
Neg ENA
No Raynaud's
Weight loss
No dysphagia
No dilated capillaries

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Tight skin but sparing fingers and hands, Monoclonal gammapathy, neg ANA, Neg ENA No Raynaud's Weight loss No dysphagia No dilated capillaries

Do not apply criteria, no hand involvement ever with skin involvement elsewhere – suspect another diagnosis

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

SLE with +ANA, anti-DNA, +centromere Ab Also finger tip ulcers, Sclerodactyly whole fingers Raynaud's, Telangiectasia, calcinosis Needing repeat esophageal dilations

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

SLE with +ANA, 0 anti-DNA, 0 +centromere Ab 3 Also finger tip ulcers, 2 Sclerodactyly whole fingers 4 Raynaud's, 3 Telangiectasia, 2 calcinosis 0 Needing repeat esophageal dilations 0

Total score 14 Patient has SLE and SSc overlap

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sjögren's with +ANA, centromere Ab +Ro, La, RF Puffy whole fingers Raynaud's, Telangiectasia, ILD

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sjögren's with +ANA, 0 centromere Ab 3 +Ro, La, RF 0 Puffy whole fingers 2 Raynaud's, 3 Telangiectasia, 2 ILD 2

Total score 12 Patient has Sjogren's and SSc overlap

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sjögren's with +ANA, centromere Ab +Ro, La, RF Puffy whole fingers Raynaud's, Telangiectasia, dilated capillaires

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sjögren's with +ANA, 0 centromere Ab 3 +Ro, La, RF 0 Puffy whole fingers 2 Raynaud's, 3 Telangiectasia, 2 dilated capillaires 2

Total score 12

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sjögren's with +ANA, centromere Ab +Ro, La, RF Puffy whole fingers Raynaud's

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Sjögren's with +ANA, 0 centromere Ab 3
+Ro, La, RF 0
Puffy whole fingers 2
Raynaud's 3

Total score 8, criteria not met for SSc

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Dermatomyositis+ ANA, +Jo1
Puffy whole fingers
Raynaud's
Digital ulcer
Dilated capillaries which resolved with treatment of myositis
Cape like Rash, photosensitivity.
ILD

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Dermatomyositis+ ANA, +Jo1 0
Puffy whole fingers 2
Raynaud's 3
Digital ulcer 2
Dilated capillaries which resolved with treatment of myositis 2
Cape like Rash, 0
photosensitivity. 0
ILD 2

Total score 11, BUT you may choose not to apply criteria if SSc overlap is not suspected and you think the features are due to dermatomyositis

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers	2
	Whole Finger, distal to MCP	4
Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Dermatomyositis+ ANA, +Jo1
Sclerodactyly distally to PIPs
Raynaud's
Dilated capillaries which resolved with treatment of myositis
Cape like Rash, photosensitivity.
ILD

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Dermatomyositis+ ANA, +jo1
Raynaud's
Digital ulcer
Dilated capillaries which resolved with treatment of myositis
Cape like Rash, photosensitivity.
ILD
Tight face and tight fingers proximal to MCPs

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2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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Finger tip lesions	Digital Tip Ulcers	2
(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Dermatomyositis+ANA, +Jo1 0
Raynaud's 3
Digital ulcer 2
Dilated capillaries which resolved with treatment of myositis 2
Cape like Rash, 0
photosensitivity. 0
ILD 2
Tight face and tight fingers proximal to MCPs 9

Total score 18
Overlap of dermatomyositis and SSc

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers+ANA, Raynaud's Dysphagia Scleroderma Renal crisis

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers 2
+ANA, 0
Raynaud's 3
Dysphagia 0
Scleroderma
Renal crisis 0

Total score 5
SSc criteria not met

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

Items	**Sub-items**	**Weight / Score**
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints		9
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(only count the highest score)	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of 9 or more are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers 2
+ANA, 0
Raynaud's 3
Dysphagia 0
Scleroderma
Renal crisis 0

Patient returns in two months with skin tightening to above the elbows and tendon friction rubs

1. These criteria are applicable to any patient considered for inclusion in a SSc study.
2. These criteria are **not applicable** to patients having a systemic sclerosis-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic chierarthropathy. Patients with '***Skin thickening sparing the fingers'*** also are not classified as having SSc.

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Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease		2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerasel [anti-ScL 70], anti-RNA polymerase III)		3
	TOTAL SCORE^:	

Patients having a total score of <u>9 or more</u> are being classified as having definite systemic sclerosis. ^ Add the maximum weight (score) in each category to calculate the total score.

Puffy fingers 2
+ANA, 0
Raynaud's 3
Dysphagia 0
Scleroderma
Renal crisis 0

Patient returns in two months with skin tightening to above the elbows 9 and tendon friction rubs 0

Total score 14
Criteria now met

Backup Slides

Early symptoms of SSc

- Raynaud's phenomenon
  - May precede skin changes and visceral disease by several years especially in limited SSc
  - In dcSSc, RP may begin shortly after or coincident with the onset of skin disease
  - SSc patients may have less hyperaemia than in primary Raynaud's due to structural vasculopathy in SSc
- Puffy fingers may be the presenting sign in dcSSc
- Malaise, fatigue, arthralgia, myalgia
- Gastroesophageal symptoms or dyspnoea may be the presenting symptoms

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Which patient does not meet 1980 ACR SSc classification criteria?

1. Sclerodactyly and digital pits and Raynaud's, positive anti-centromere
2. Sclerodactyly and dysphagia and pulmonary fibrosis
3. Sclerodactyly, Raynaud's, anti-centromere, dysphagia, dilated nailfold capillaries, PAH and calcinosis
4. Modified Rodnan skin score of 20 including finger involvement

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23:581-90

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Which patient does not meet 1980 ACR SSc classification criteria?

1. Sclerodactyly and digital pits and Raynaud's, positive anti-centromere
2. Sclerodactyly and dysphagia and pulmonary fibrosis
3. **Sclerodactyly, Raynaud's, anti-centromere, dysphagia, dilated nailfold capillaries, PAH and calcinosis**
4. Modified Rodnan skin score of 20 including finger involvement

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23:581-90

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LeRoy criteria (2001): Classification criteria early SSc

lSSc	Raynaud's phenomenon (objective) Plus any one: SSc-type nailfold capillary pattern or SSc selective autoantibodies
	OR
	Raynaud's phenomenon (subjective only) Plus both SSc-type nailfold capillary pattern and SSc selective autoantibodies
lcSSc	Criteria for lSSc plus distal cutaneous changes
dcSSc	Criteria for lSSc plus proximal cutaneous changes

LeRoy EC and Medsger TA, Jr. *J Rheumatol* 2001; 28:1573-6.

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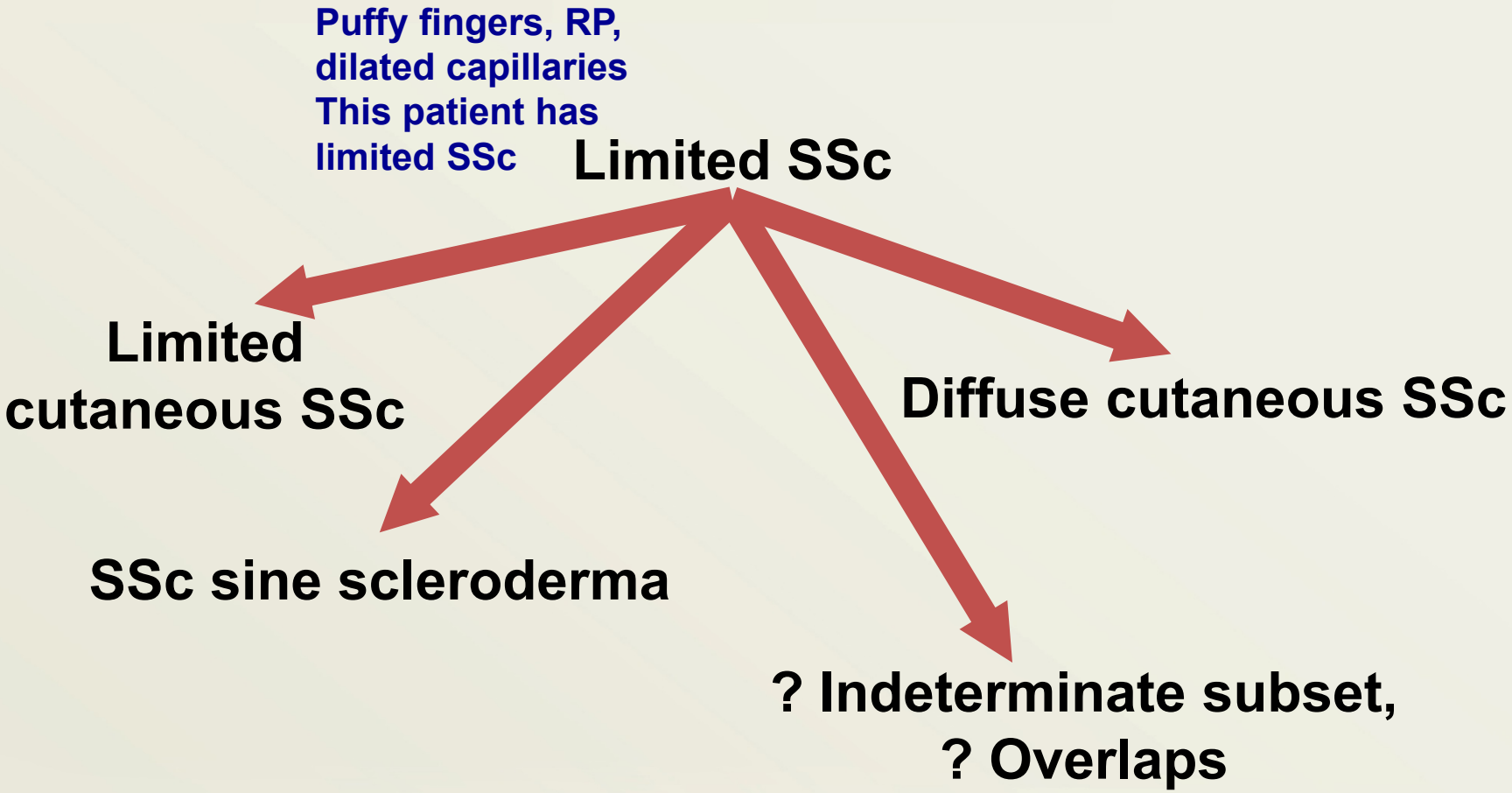
Subsets of SSc



Adapted from Hachulla E, *et al*. *Clinical Rev Allergy Immunol* 2010; Epub ahead of print.

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RHEUMATOLOGY

Rheumatology 2016;55:1906–1910
doi:10.1093/rheumatology/kew224
Advance Access publication 9 June 2016

Guidelines

BSR and BHPR guideline for the treatment of systemic sclerosis

Christopher P. Denton[1], Michael Hughes[2], Nataliya Gak[1], Josephine Vila[3], Maya H. Buch[4], Kuntal Chakravarty[1], Kim Fligelstone[1], Luke L. Gompels[5], Bridget Griffiths[3], Ariane L. Herrick[2], Jay Pang[6], Louise Parker[7], Anthony Redmond[4], Jacob van Laar[8], Louise Warburton[9] and Voon H. Ong[1] on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group

Key words: scleroderma, systemic sclerosis, management, Raynaud's phenomenon, lung fibrosis, pulmonary hypertension, digital ulcers

GUIDELINES

Executive Summary

Scope and purpose

SSc is a complex, multi-organ disease that requires a comprehensive multidisciplinary guideline. This is a short summary of the guideline, which is available in full as supplementary material at *Rheumatology* Online. Each recommendation is graded for level of evidence (I-IV) and strength (A-D).

Eligibility and exclusion criteria

Patients are classified as having SSc based on current classification criteria (ACR/EULAR 2013 [1]). Other scleroderma spectrum diseases are not included in this document.

NICE has accredited the process used by the BSR to produce its treatment of systemic sclerosis guidance. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

Part A: general approach to SSc management

Figure 1 summarizes a general approach to management of SSc.

Importance of early diffuse SSc: current priorities and approach

Management of early diffuse cutaneous SSc (dcSSc) should occur within the framework of a multidisciplinary team.

Recommendations in management of early SSc

(i) Early recognition and diagnosis of dcSSc is a priority, with referral to a specialist SSc centre (III, C).

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Submitted 11 January 2016; revised version accepted 12 April 2016

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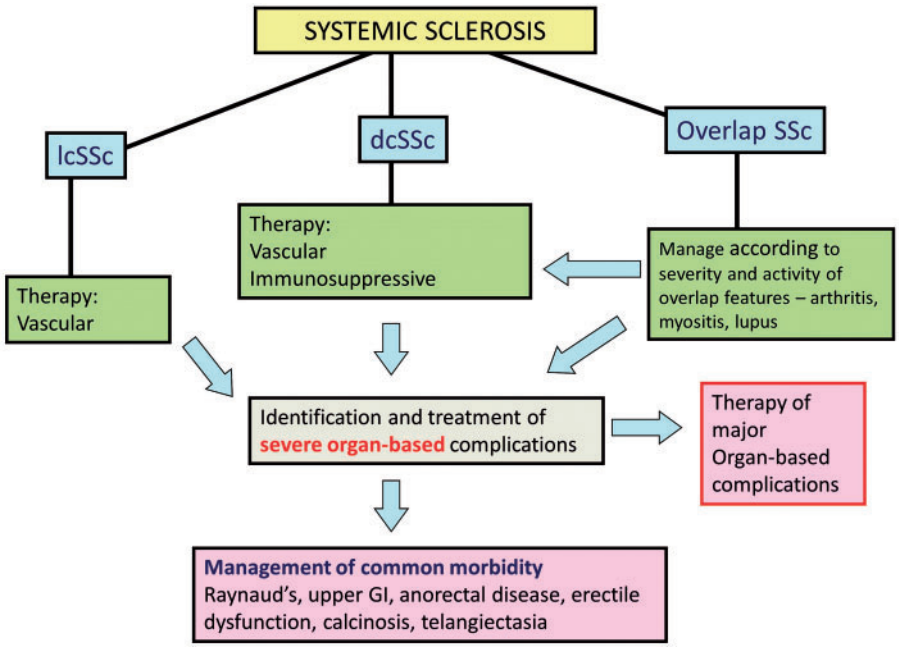
Fig. 1 Overview of management of SSc



The principles of current management of SSc are summarized. Once a confirmed diagnosis is established, all patients can be designated as either lcSSc or dcSSc subset based upon the extent of skin thickening. Proximal skin involvement, involving skin of trunk or proximal limbs, is designated diffuse. Cases with overlap disease should be identified so that overlap features may be treated concurrently with SSc. All patients require symptomatic treatment, and both limited and diffuse cases should be treated for vascular manifestations. Active, early dcSSc requires immunosuppressive treatment. In all cases of SSc, vigilant follow-up to determine significant organ-based complications is mandatory. dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; GI: gastrointestinal.

(ii) Patients with early dcSSc should be offered an immunosuppressive agent: MTX, MMF or i.v. CYC (III/C), although the evidence base is weak. Some patients might later be candidates for autologous haemopoietic stem cell transplant (ASCT; see below).
(iii) D-Pen is not recommended (IIa/C).
(iv) ASCT may be considered in some cases, particularly where there is risk of severe organ involvement, balancing concerns about treatment toxicity (IIa/C).
(v) Skin involvement may be treated with either MTX (II, B) or MMF (III, C). Other options include CYC (III, C), oral steroid therapy (in as low a dose as possible to suppress symptoms, and with close monitoring of renal function; III, C) and possibly rituximab (III, C).
(vi) AZA or MMF should be considered after CYC to maintain improvement in skin sclerosis and/or lung function (III, C).

Part B: key therapies and treatment of organ-based disease

RP and digital ulcers

RP is almost universal and can be treated by vasodilators, but benefit must be balanced against side-effects. Around half of patients with SSc report a history of digital ulceration that reflects more structural vasculopathy. Severe digital ulcers (DUs) are those causing or threatening tissue destruction or when three or more occur in 1 year. These should be considered for advanced therapy, such as sildenafil, iloprost or bosentan [2].

Recommendations for RP in SSc

(i) First-line treatments are calcium channel blockers (Ia, A) and angiotensin II receptor antagonists (Ib, C).
(ii) Other treatments that may be considered are: selective serotonin reuptake inhibitors, α-blockers and statin therapy (III, C).
(iii) Phosphodiesterase type 5 inhibitors are being used increasingly for SSc-related RP (IIa, C).
(iv) Intravenous prostanoid (e.g. iloprost; Ia, B) and digital (palmar) sympathectomy (with or without botulinum toxin injection) should be considered in severe and/or refractory cases (III, D).

Recommendations for DUs in SSc

(i) DUs require integrated management by a multidisciplinary team; management includes local and systemic treatment (III, C).
(ii) Oral vasodilator treatment should be optimized, analgesia optimized and any infection promptly treated (III, C).

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(iii) Sildenafil should now be used before considering i.v. prostanoids and bosentan, in line with the current National Health Service (NHS) England Clinical Commissioning policy [3] (I, A).
(iv) In severe active digital ulceration, patients should receive i.v. prostanoid (Ia, B). In patients with recurrent, refractory DUs, a phosphodiesterase type 5 inhibitor (IIa, B) or i.v. prostanoid (Ia, B) and an endothelin receptor antagonist (including bosentan; Ia, B) should be considered.
(v) Digital (palmar) sympathectomy (with or without botulinum toxin injection) may also be considered in severe and/or refractory cases (III, D).

Lung fibrosis

Up to 80% of SSc patients will develop interstitial lung disease, but this may be mild and stable. Immunosuppression should be considered when extensive or progressive disease is confirmed.

Recommendations for lung fibrosis in SSc

(i) All SSc cases should be evaluated for lung fibrosis. Treatment is determined by the extent and severity and the likelihood of progression to severe disease (I, A).
(ii) CYC by i.v. infusion is recommended (I, A/B), and MMF may also be used as an alternative or after CYC (II, B).

Pulmonary arterial hypertension

For patients living in England, treatments are initiated through a designated Pulmonary Hypertension Centre (see NHS England A11/S/a) according to the national commissioning policy for treatment of pulmonary arterial hypertension (PAH; NHS England/A11/P/b and NHS Commissioning Board (NHSCB)/A11/P/a), reflecting expert recommendations [4].

Recommendations for PAH in SSc

(i) Diagnosis should be based upon results of full evaluation of PAH, including right heart catheterization and evaluation of concomitant SSc-related cardiac or lung disease (I, A).
(ii) Therapies licensed for PAH should be used in the UK Pulmonary Hypertension Centres, taking account of the agreed commissioning policies (I, A/B).

Gut disease

Gastro-oesophageal reflux is near universal and needs treatment. Other gastrointestinal (GI) manifestations include constipation, bloating, small intestinal bacterial overgrowth, altered bowel habit and anorectal incontinence (overall management covered elsewhere [5]).

Recommendations for GI manifestations in SSc

The following therapeutic approaches and drugs are considered by experts to be of value in treatment of GI tract complications of SSc.

(i) Proton pump inhibitors and histamine H2 receptor antagonists are recommended for treatment of gastro-oesophageal reflux and dysphagia and may require long-term administration (III, C).
(ii) Prokinetic dopamine antagonists may be used for dysphagia and reflux (III, C).
(iii) Parenteral nutrition should be considered for patients with severe weight loss refractory to enteral supplementation (III, C).
(iv) Intermittent broad-spectrum oral antibiotics (e.g. ciprofloxacin) are recommended for intestinal overgrowth, and rotational regimes may be helpful (III, C).
(v) Anti-diarrhoeal agents (e.g. loperamide) or laxatives may be used for symptomatic management of diarrhoea or constipation that often alternate as clinical problems (III, C).

Renal complications

SSc renal crisis (SRC) causes severe hypertension and acute kidney injury and without treatment is often lethal. It affects 5–10% of SSc patients, predominantly the diffuse subset.

Recommendations for treatment of SRC

(i) Patients at risk of SRC should be followed closely and their blood pressure monitored at least weekly (III, C).
(ii) Prompt recognition of SRC and initiation of therapy with an angiotensin-converting enzyme inhibitor offers the best opportunity for a good outcome (III, C).
(iii) Other anti-hypertensive agents may be considered for management of refractory hypertension in conjunction with an angiotensin-converting enzyme inhibitor in SRC (III, C).

Cardiac disease

Clinically evident cardiac involvement includes diastolic or systolic heart failure, arrhythmia and conduction disturbances and has a significant mortality.

Recommendations for treatment of cardiac manifestations of SSc

Although the published evidence base is limited, experts have recommended the following treatment approach for cardiac complications of SSc.

Systolic heart failure

(i) Consider immunosuppression with or without a pacemaker (IV, D).
(ii) Consider the potential benefit of an implantable cardioverter defibrillator (III, D).
(iii) Angiotensin-converting enzyme inhibitors and carvedilol. Selective β-blockers may be considered, but consider aggravation of RP (IV, D).

Diastolic heart failure with preserved left ventricular ejection fraction

(i) Diuretics, including spironolactone and furosemide (IV, D).

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(ii) Calcium channel blockers have been shown to reduce the frequency of systolic heart failure in SSc with investigational evidence of cardiac abnormalities (III, D).

Skin manifestations

Treatment of skin thickening, assessed by modified Rodnan skin score, is central to management of dcSSc treatment, and pruritus is common and troublesome in early stage disease.

Recommendations for skin manifestations in SSc

(i) Practical approaches to ensure adequately moisturized skin are essential, especially moisturizers that are lanolin based (III, C).
(ii) Antihistamines are often used for itch (III, C).
(iii) Current treatment options for telangiectasia include skin camouflage and laser or intense pulsed light therapy (III, C).

Calcinosis in SSc

There is a very limited evidence base (mainly case reports and small series) to guide clinicians on the management of calcinosis in patients with SSc.

Recommendations for treatment of calcinosis in SSc

(i) Calcinosis complicated by infection should be recognized early and treated with appropriate antibiotic therapy (III, D).
(ii) Surgical intervention should be considered for severe, refractory calcinosis, which is severely impacting upon functional ability and quality of life (III, D).

Musculoskeletal manifestations

Musculoskeletal involvement includes tendinopathy, joint contractures and, in some cases, overlap arthritis.

Recommendations for musculoskeletal manifestations in SSc

(i) Musculoskeletal manifestations of SSc may benefit from immunomodulatory treatments given for other complications, such as skin disease (III, C).
(ii) When arthritis or myositis is more severe, generally in the context of an overlap SSc syndrome, management is in line with similar clinical conditions occurring outside the context of SSc (III, C).

ASCT as a treatment for poor prognosis early dcSSc

Haematopoietic stem cell transplant registry data, several case reports and pilot studies in the USA and Europe in dcSSc demonstrated a rapid clinical improvement, but with important treatment-related mortality [6].

Recommendation for ASCT in SSc

(i) Current evidence supports use of ASCT in poor-prognosis diffuse SSc where patients do not have severe internal organ manifestations that render this treatment option highly toxic (Ib, B).

Non-drug interventions

Although the evidence base is limited, non-drug interventions may have merit and are well tolerated.

Recommendation for non-drug interventions in SSc

(i) Specialist experience of SSc cases is likely to make non-drug interventions more effective, and these approaches are popular with patients and can be expected to impact positively on the disease. More research is needed in this area (III, D).

Part C: service organization and delivery within NHS England

SSc should be diagnosed promptly, investigated appropriately and managed within an integrated system of primary, secondary and tertiary level care.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: C.P.D. has been a consultant to Actelion, GlaxoSmithKline, Bayer, Inventiva, Takeda and Roche and received research grants from CSL Behring, Novartis and Actelion. J.v.L. has been a consultant for MSD, Pfizer, Roche, BMS and Eli Lilly. A.L.H. has been a consultant to Actelion and Apricus, has spoken at meetings sponsored by Actelion and received research funding from Actelion. All other authors have declared no conflicts of interest.

Supplementary data

The full guideline is available as supplementary data at *Rheumatology* Online.

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ARTHRITIS & RHEUMATISM
Vol. 65, No. 11, November 2013, pp 2737–2747
DOI 10.1002/art.38098
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Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
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SPECIAL ARTICLE

2013 Classification Criteria for Systemic Sclerosis

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an external data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

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This article is published simultaneously in the November 2013 issue of *Annals of the Rheumatic Diseases*.

Supported by the American College of Rheumatology and the European League Against Rheumatism. Dr. Khanna's work was supported by the Scleroderma Foundation (New Investigator award) and the NIH (National Institute of Arthritis and Musculoskeletal and Skin Diseases grant K24-AR-063120). Dr. Johnson's work was supported by the Canadian Institutes of Health Research (Clinician Scientist award) and the Norton-Evans Fund for Scleroderma Research.

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Objective. **The 1980 American College of Rheumatology (ACR) classification criteria for systemic sclerosis (SSc) lack sensitivity for early SSc and limited cutaneous SSc. The present work, by a joint committee of the ACR and the European League Against Rheumatism (EULAR), was undertaken for the purpose of developing new classification criteria for SSc.**

Methods. **Using consensus methods, 23 candidate items were arranged in a multicriteria additive point system with a threshold to classify cases as SSc. The classification system was reduced by clustering items and simplifying weights. The system was tested by 1) determining specificity and sensitivity in SSc cases and controls with scleroderma-like disorders, and 2) validating against the combined view of a group of experts on a set of cases with or without SSc.**

Results. **It was determined that skin thickening of the fingers extending proximal to the metacarpophalangeal joints is sufficient for the patient to be classified as having SSc; if that is not present, 7 additive items apply, with varying weights for each: skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud's phenomenon, and SSc-related autoantibodies. Sensitivity and specificity in the validation sample were, respectively, 0.91 and 0.92 for the new classification criteria and 0.75 and 0.72 for the 1980 ACR classification criteria. All selected cases were classified in accordance with consensus-based expert opinion. All cases classified as SSc accord-**

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Dr. Khanna has received consulting fees from Bayer, Bristol-Myers Squibb, Digna Biotech, InterMune, Gilead, and Merck (less than $10,000 each) and consulting and speaking fees from Actelion and United Therapeutics (more than $10,000 each). Dr. Matucci-Cerinic has received consulting fees, speaking fees, and/or honoraria from Bristol-Myers Squibb, Pfizer, and Actelion (less than $10,000 each). Dr. Distler has received consulting fees, speaking fees, and/or honoraria from Bayer, Pfizer, Ergonex, Bristol-Myers Squibb, Sanofi-Aventis, Sinoxa Pharma, United BioSource, Medac, Swedish Orphan Biovitrium, Boehringer Ingelheim Pharma, Novartis, and Active Biotech (less than $10,000 each) and from Actelion and 4D Science (more than $10,000 each); he also has a patent for the use of microRNA-29 for the treatment of systemic sclerosis. Dr. Allanore has received consulting fees, speaking fees, and/or honoraria from Roche, Actelion, and Pfizer (less than $10,000 each). Dr. Furst has received consulting fees, speaking fees, and/or honoraria from Actelion, Gilead, and Genentech/Roche (less than $10,000 each). Dr. Gabrielli has received research grants from Actelion, Roche, Abbott, and Pfizer. Dr. Mayes has received consulting fees, speaking fees, and/or honoraria from Actelion, Practice Point Communications, and Medtelligence (less than $10,000 each) and receives royalties from Oxford University Press for *The Scleroderma Book* and from Henry Stewart Talks for a video of a prerecorded lecture on scleroderma. Dr. van Laar has received honoraria from Roche, Genentech, Pfizer, Abbott, Menarini, and Miltenyi Biotech (less than $10,000 each) and research grants from Roche/Genentech and Trubion Pharmaceuticals. Dr. Inanc has received consulting fees, speaking fees, and/or honoraria from Actelion Turkey, Bayer Turkey, and GlaxoSmithKline Turkey (less than $10,000 each). Dr. Kowal-Bielecka has received consulting fees, speaking fees, and/or honoraria from Actelion and Pfizer (less than $10,000 each). Dr. Veale has received consulting fees, speaking fees, and/or honoraria from Pfizer, UCB, MSD, and Roche (less than $10,000 each). Dr. Vonk has received consulting fees, speaking fees, and/or honoraria from Actelion, Pfizer, GlaxoSmithKline, and United Therapeutics (less than $10,000 each). Dr. Collier owns stock or stock options in Amgen. Dr. Herrick has received consulting fees, speaking fees, and/or honoraria from Actelion (less than $10,000 each). Dr. Sierakowski has received consulting fees, speaking fees, and/or honoraria from Roche, Pfizer, Abbott, MSD, GlaxoSmithKline, and Egis Pharmaceuticals (less than $10,000 each). Dr. Silver has received consulting fees, speaking fees, and/or honoraria from Genentech and Actelion (less than $10,000 each).

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Submitted for publication January 26, 2013; accepted in revised form July 16, 2013.

ing to the 1980 ACR criteria were classified as SSc with the new criteria, and several additional cases were now considered to be SSc.

***Conclusion*. The ACR/EULAR classification criteria for SSc performed better than the 1980 ACR criteria for SSc and should allow for more patients to be classified correctly as having the disease.**

Introduction

Systemic sclerosis (SSc; scleroderma) is a heterogeneous disease whose pathogenesis is characterized by 3 hallmarks: small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction leading to increased deposition of extracellular matrix (1). The clinical manifestations and the prognosis of SSc vary, with the majority of patients having skin thickening and variable involvement of internal organs. Subsets of SSc can be discerned, i.e., limited cutaneous SSc, diffuse cutaneous SSc, and SSc without skin involvement (1).

In the absence of a diagnostic test proving the absence or presence of SSc, several sets of classification criteria have been developed (2–6). The purpose of classification criteria is to enroll, in research studies, patients who in fact have the disease as determined using a uniform definition (7). Classification criteria are not synonymous with diagnostic criteria but will almost always mirror the list of criteria that are used for diagnosis (7). However, classification criteria generally are more standardized and less inclusive than physician diagnosis.

The current standard classification criteria for SSc are the 1980 preliminary criteria for the classification of systemic sclerosis (scleroderma), developed by the American College of Rheumatology (ACR) (2–4,8). These classification criteria were developed using patients with longstanding SSc. As a consequence, patients with early SSc and ~20% of patients with limited cutaneous disease do not meet the criteria and are excluded from clinical studies (1,9,10). Since the development of the 1980 criteria, knowledge regarding SSc-related autoantibodies has improved (11–13). In addition, characteristic nailfold capillary changes have been found to be associated with SSc, and nailfold capillaroscopy is widely accepted as a diagnostic tool (10,14–17). In 1988, LeRoy et al proposed new criteria that included clinical features, autoantibodies, and capillaroscopy results, highlighting the differences between the 2 main SSc subsets (11). In 2001, LeRoy and Medsger proposed to revise the classification criteria to include "early" SSc, using nailfold capillary pattern and SSc-related autoantibodies (6). It also has been demonstrated that the addition of nailfold capillary abnormalities and telangiectasias to the ACR SSc criteria improves their sensitivity (9,18).

Because of the insufficient sensitivity of the 1980 criteria and advances in knowledge about SSc, the ACR and the European League Against Rheumatism (EULAR) established a committee to provide a joint proposal for new classification criteria for SSc. The aims were to develop criteria that 1) encompass a broader spectrum of SSc including patients whose disease is in the early stage as well as those in the late stage; 2) include vascular, immunologic, and fibrotic manifestations; 3) are feasible to use in daily clinical practice; and 4) are in accordance with criteria used for diagnosis of SSc in clinical practice (7). These criteria are intended to be used by rheumatologists, researchers, national and international drug agencies, pharmaceutical companies, or any others involved in studies of SSc. Our objective was to develop a set of criteria that would enable identification of individuals with SSc for inclusion in clinical studies, being more sensitive and specific than previous criteria.

Methods

Overview. The development and testing of the classification system for SSc was based on both data and expert clinical judgment. First, candidate items for the classification criteria were generated using consensus methods and evaluated using existing databases (19,20). Second, multicriteria decision analysis was used to reduce the number of candidate criteria and assign preliminary weights (21). The classification system was repeatedly tested and adapted using prospectively collected SSc cases and non-SSc controls, and compared against expert clinical judgment. Third, the classification criteria were tested in a validation cohort and tested against preexisting criteria sets.

Item generation and reduction. One hundred sixty-eight candidate criteria were identified through 2 Delphi exercises. A 3-round Delphi exercise and a face-to-face consensus meeting using nominal group technique facilitated reduction of the 168 items to 23 (19). Using a random sample of existing databases (SSc [n = 783] and control patients with diseases similar to SSc [n = 1,071], all based on physician diagnosis), the candidate criteria were found to have good discriminative validity (20).

Item reduction and weighting. *Draft classification system.* A face-to-face meeting of 4 European and 4 North American SSc experts was held to further reduce items and assign preliminary weights using multicriteria decision analysis. The number of experts was limited in advance to 8, and they were invited based on geographic representation, knowledge from a scientific and a practical diagnostic viewpoint, and availability. At the meeting, the experts determined by consensus to which cases the criteria should be and should not be

applied, and which items are sufficient to allow classification of a patient as having SSc (sufficient criteria). They then participated in a multicriteria decision analysis to further reduce the 23 items and assign preliminary weights (21). The experts were presented hypothetical pairs of cases with 2 of the 23 items at a time (e.g., Raynaud's phenomenon positive *and* abnormal nailfold capillaries absent versus Raynaud's phenomenon negative *and* abnormal nailfold capillaries present, all other manifestations being considered equal) and they were asked to individually vote electronically on which case of the pair was more likely to be SSc. The result of the votes was immediately presented. If there was no complete agreement among the experts, considerations were discussed and a second round of voting was conducted. As a result of the repeated choices between 2 alternative cases, items were ranked, and weights for the items were derived using 1000Minds decision-making software (21). Additional details about the methods are available in ref. 22.

Initial threshold identification. The committee prepared summaries of 45 SSc cases, with a concentration of cases that were difficult to classify. These were presented to 22 SSc experts who classified the cases as definite SSc or not. The draft classification system derived from the multicriteria decision analysis was applied to the 45 cases, resulting in a score for each case. The ranking of cases by the SSc experts and the ranking of cases based on the scores provided with the draft scoring system were examined. Higher scores in the scoring system were expected to relate to a higher probability that the experts would classify the case as SSc. Using these results, an initial threshold score for SSc was identified.

Reduction and testing of iterative changes. In the next step, the committee reduced the number of items, simplified the weights, and modified the threshold score. First, data on the candidate items were prospectively collected at 13 SSc centers in North America and 10 in Europe, using standardized case record forms. Data from 368 consecutive patients with SSc (diagnosis based on physician opinion) were collected, of whom half were to have had SSc for a maximum of 2 years (based on the time from the first non-Raynaud's symptom) in order to include early SSc. Data from 237 consecutive control patients with a scleroderma-like disorder (eosinophilic fasciitis [also called Shulman's disease or diffuse fasciitis with eosinophilia], scleromyxedema, systemic lupus erythematosus, dermatomyositis, polymyositis, primary Raynaud's phenomenon, mixed connective tissue disease, undifferentiated connective tissue disease, generalized morphea, nephrogenic systemic sclerosis, and diabetic cheiroarthropathy) were also collected. From these 605 patients a random sample of 100 SSc cases and 100 controls (50% from North America and 50% from Europe) was selected to form the derivation sample. The remaining 268 cases and 137 controls formed the validation sample. Institutional research ethics board approval was obtained for the collection of patient data.

The committee then met and made iterative changes to the draft system, which they continually applied in real time to the derivation cohort derived as described above. Using the derivation cohort, the scoring system was simplified by removing items that occurred with low frequency or were redundant, by aggregating similar items and then transforming the weights to obtain single digits. The preliminary score threshold was adjusted to account for the weight simplification. The impact of all proposed changes was evaluated by assessing changes to sensitivity and specificity of the criteria in the derivation cohort. The reference standard to test the sensitivity and specificity was the diagnosis by the SSc expert who submitted the case(s) and control(s).

At the same time, the changes in the classification system were also tested in 38 difficult-to-classify cases. Consequently, weights of some items were adjusted to align the scoring system with the reference standard formed by the opinions of the SSc experts as to which cases were to be classified as having SSc.

Validation. The final classification system was independently tested using the validation sample of SSc cases and controls. Sensitivity and specificity were calculated for the 1980 ACR preliminary classification criteria for SSc (3), the classification criteria proposed by LeRoy and Medsger in 2001 (6), and the newly developed classification criteria. Exact binomial confidence limits were calculated for sensitivity and specificity. The ACR criteria and LeRoy/Medsger criteria were compared with the new criteria using 2×2 tables with McNemar's chi-square test and continuity correction. The criteria sets were also tested separately using only the subgroup of patients with a disease duration of ≤ 3 years. Further, the classification system was validated against the expert consensus on the set of 38 selected cases.

Results

Draft classification system. The experts concluded that "skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints" was sufficient to classify a subject as having SSc. Further, patients with "skin thickening sparing the fingers" are classified as not having SSc. It was agreed that the criteria should be applied to any patient considered for inclusion in an SSc study, without further specifications. Items with relatively low weights were deleted, and items considered to be from a similar domain were clustered (e.g., fingertip lesions encompasses ulcers and pitting scars; lung involvement encompasses interstitial lung disease and pulmonary hypertension). Using conjoint analysis, the number of items was reduced from 23 to 14 and all items were assigned weights. The 14 resulting items (with weights) were as follows: bilateral skin thickening of the fingers (sclerodactyly) (weighted 14 if distal to a proximal interphalangeal joint only, 22 if whole finger), puffy fingers (weighted 5), fingertip lesions (weighted 16 if pitting scars or 9 if digital ulcers), finger flexion contractures (weighted 16), telangiectasia (weighted 10), abnormal nailfold capillaries (weighted 10), calcinosis (weighted 12), Raynaud's phenomenon (weighted 13), tendon or bursal friction rubs (weighted 21), interstitial lung disease/pulmonary fibrosis (weighted 14), pulmonary arterial hypertension (weighted 12), scleroderma renal crisis (weighted 11), esophageal dilation (weighted 7), and SSc-related autoantibodies (weighted 15 if anticentromere antibody pres-

Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)*

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere	3
	Anti–topoisomerase I	
	Anti–RNA polymerase III	

* These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).
† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥ 9 are classified as having definite SSc.

Table 2. Definitions of items/sub-items in the American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)

Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits—a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.
Fingertip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischemia, rather than trauma or exogenous causes.
Telangiectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with systemic sclerosis	Enlarged capillaries and/or capillary loss with or without pericapillary hemorrhages at the nailfold. May also be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterization according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of "Velcro" crackles on auscultation, not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase color change in finger(s) and often toe(s) consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
SSc-related autoantibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, anti–topoisomerase I antibody (also known as anti–Scl-70 antibody), or anti–RNA polymerase III antibody. Positive according to local laboratory standards.

Table 3. Characteristics of the derivation sample and the validation sample*

Item	Derivation sample			Validation sample		
	SSc (n = 100)	Scleroderma-like disorder (n = 100)	*P*	SSc (n = 268)	Scleroderma-like disorder (n = 137)	*P*
Age, mean ± SD years	55 ± 13	51 ± 15	0.05	54 ± 13	52 ± 15	0.17
Female	86 (86)	79 (79)	0.25	221 (83)	101 (75)	0.08
Region						
North America	50	50	–	191 (68)	91 (32)	–
Europe	50	50		77 (63)	46 (37)	0.32
Time since onset of Raynaud's phenomenon, median (IQR) years	13 (7–18)	12 (4–18)	0.42	9 (5–18)	10 (4–22)	0.40
Time since first non-Raynaud's symptom, median (IQR) years	10 (4–13)	9 (2–14)	0.58	7 (3–12)	7 (3–15)	0.89
Time since diagnosis, median (IQR) years	8 (3–12)	6 (1–9)	0.10	5 (2–11)	4 (1–7)	0.016
Scleroderma-like disorders						
Systemic lupus erythematosus	–	28 (28)	–	–	32 (23)	–
Polymyositis/dermatomyositis	–	23 (23)	–	–	21 (15)	–
Primary Raynaud's phenomenon	–	19 (19)	–	–	7 (5)	–
Mixed connective tissue disease	–	9 (9)	–	–	14 (10)	–
Undifferentiated connective tissue disease	–	8 (8)	–	–	17 (12)	–
Eosinophilic fasciitis	–	6 (6)	–	–	16 (12)	–
Nephrogenic sclerosing fibrosis	–	3 (3)	–	–	3 (2)	–
Generalized morphea	–	5 (5)	–	–	8 (6)	–
Scleromyxedema	–	1 (1)	–	–	3 (2)	–
Graft-versus-host disease	–	3 (3)	–	–	3 (2)	–
Other diagnoses	–	8 (8)	–	–	13 (9)	–
Manifestations†	–	–	–	–	–	–
Raynaud's phenomenon	91 (91)	49 (49)	<0.0001	257 (96)	63 (46)	<0.0001
Autoantibodies	68 (68)	7 (7)	<0.0001	137 (51)	15 (11)	<0.0001
Anticentromere antibody	33 (33)	5 (5)	<0.0001	41 (15)	8 (6)	0.0057
Anti–topoisomerase I	34 (34)	1 (1)	<0.0001	69 (26)	7 (5)	<0.0001
Anti–RNA polymerase III	2 (2)	1 (1)	1.0	27 (10)	0	<0.0001
Puffy fingers	61 (61)	17 (17)	<0.0001	169 (63)	24 (18)	<0.0001
Abnormal nailfold capillaries	54 (54)	24 (24)	<0.0001	146 (54)	51 (37)	0.0010
Dilated vessels	37 (37)	28 (28)	0.08	124 (46)	34 (25)	0.0080
Avascular areas	21 (21)	11 (11)	0.08	86 (32)	9 (7)	<0.0001
Hemorrhages	12 (12)	9 (9)	0.64	63 (24)	8 (6)	<0.0001
Digital tip ulcers	53 (53)	8 (8)	<0.0001	108 (40)	12 (9)	<0.0001
Pitting scars	53 (53)	5 (5)	<0.0001	105 (39)	5 (4)	<0.0001
PAH or ILD	48 (48)	14 (14)	<0.0001	138 (52)	14 (10)	<0.0001
PAH	44 (44)	10 (10)	<0.0001	20 (7)	2 (1)	0.012
ILD	12 (12)	4 (4)	0.037	131 (49)	12 (9)	<0.0001
Telangiectasia	35 (35)	10 (10)	<0.0001	68 (25)	13 (9)	0.0002
Skin thickening of fingers proximal to MCP joints	26 (26)	1 (1)	<0.0001	105 (39)	6 (4)	<0.0001
Skin thickening of fingers distal to MCP joints	5 (5)	38 (38)	<0.0001	178 (66)	24 (18)	<0.0001

* Data were prospectively collected on 605 consecutive patients with systemic sclerosis (SSc) or a scleroderma-like disorder (see Methods); half of the SSc patients at each site were to have early SSc. A random sample of 100 SSc cases and 100 controls, 50% from North America and 50% from Europe, was selected to form the derivation sample, and the remaining patients formed the validation sample. Except where indicated otherwise, values are the number (%). IQR = interquartile range; PAH = pulmonary arterial hypertension; ILD = interstitial lung disease; MCP = metacarpophalangeal.

† Listed in order of frequency of occurrence in the SSc derivation sample.

ent, anticentromere pattern seen on antinuclear antibody testing, or anti–topoisomerase I [also called anti–Scl-70] or anti–RNA polymerase III present).

Initial threshold identification. Comparison of the case ranking from the scoring system and by the experts revealed that most of the experts (≥75%) considered the cases with a score of >55 (except for 1 case) to be SSc. Similarly, most experts (≥88%) considered cases with a score of <40 not to be SSc. With scores between 40 and 55 there was more diversity of opinion. Thus, it was concluded that the initial threshold would be a score of ≥56.

Reduction and testing of iterative changes. The 14 items in the scoring system were reduced to 9 while

Table 4. Sensitivity and specificity of the 2013 SSc classification criteria and previous SSc classification criteria, overall and in early SSc*

	Derivation sample (n = 200)		Validation sample (n = 405)		Validation sample, disease duration ≤3 years (n = 100)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
1980 ACR SSc criteria	0.80 (0.72–0.87)	0.77 (0.68–0.84)	0.75 (0.70–0.80)	0.72 (0.64–0.79)	0.75 (0.70–0.80)	0.72 (0.63–0.79)
2001 LeRoy/Medsger SSc criteria	0.76 (0.68–0.84)	0.69 (0.68–0.84)	0.75 (0.70–0.80)	0.78 (0.70–0.85)	0.80 (0.69–0.88)	0.76 (0.53–0.92)
2013 ACR/EULAR SSc criteria	0.95 (0.90–0.98)	0.93 (0.86–0.97)	0.91 (0.87–0.94)	0.92 (0.86–0.96)	0.91 (0.83–0.96)	0.90 (0.70–0.99)

* SSc = systemic sclerosis; 95% CI = 95% confidence interval; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism.

maintaining sensitivity and specificity in the derivation sample. The items deleted were finger flexion contractures, calcinosis, tendon or bursal friction rubs, renal crisis, and esophageal dilation. Puffy fingers and sclerodactyly were combined into one item, and pulmonary arterial hypertension and interstitial lung disease were also combined into one item, resulting in 7 items for the scoring system. In the derivation sample, with reduction of the 14 items to 7, the sensitivity and specificity were 0.93 and 0.94, respectively. Weights were simplified by dividing each weight by 5 and rounding to the nearest integer. The threshold for this simplified scoring system was determined to be 9. The resulting sensitivity and specificity were 0.97 and 0.88, respectively.

Weights were further adjusted to align the scoring system with the experts' opinions (SSc or not SSc) on each of the 38 difficult-to-classify cases. To improve the specificity of the classification criteria, an exclusionary criterion was added: patients with a diagnosis that better explains their manifestations should not be classified as having SSc. These revisions resulted in the correct classification of all patient profiles judged to have SSc by the majority of experts.

The SSc classification criteria. The new classification criteria are presented in Table 1. The table shows the 1 criterion that, if present, is sufficient for classification as SSc, the 2 exclusionary criteria, and the 7 items with a combined threshold above which cases are classified as SSc. The classification criteria may be applied to patients who may have SSc and are being considered for inclusion in an SSc study. As noted above, they are *not to be applied* to patients who have a scleroderma-like disorder that better explains their manifestations; and patients with "*skin thickening sparing the fingers*" are not classified as having SSc.

If a patient has skin thickening of the fingers of both hands that extends proximal to the metacarpophalangeal joints, the classification system assigns 9 points for this one item alone, which is sufficient to classify the patient as having SSc with no further application of the point system needed. Otherwise, the point system is applied by adding the scores for manifestations that are "positive." The items are skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nailfold capillaries, pulmonary arterial hypertension and/or interstitial lung disease, Raynaud's phenomenon, and SSc-related autoantibodies. Two items, skin thickening of the fingers and fingertip lesions, include 2 different possible manifestations. If a patient has both manifestations, the score for the category is the higher score of the 2 manifestations. For example, in the item skin thickening of the fingers, if a patient has both manifestations, i.e., puffy fingers (weighted 2) and sclerodactyly (weighted 4), the total score for the item would be 4. The maximum possible score is 19, and patients with a score of ≥9 are classified as having SSc. The definitions of the items used in the criteria are provided in Table 2.

Validation. Table 3 shows the characteristics of the validation sample (268 patients with SSc, 137 controls). The sensitivity and specificity of the new SSc classification criteria were compared with those of the 1980 ACR classification criteria and the classification criteria proposed by LeRoy and Medsger, and the results are shown in Table 4. The sensitivity and specificity of the new SSc criteria were, respectively, 0.91 and 0.92 in the validation sample. The new criteria performed better than the 2 earlier classification schemes in terms of sensitivity and specificity ($P = 0.01$ versus the 1980 ACR criteria, $P = 0.004$ versus the LeRoy/Medsger criteria). The area under the receiver operating characteristic curve of the classification system tested against presence of SSc in the validation sample was 0.81 (95% confidence interval 0.77–0.85). The performance of the new criteria in patients with disease of ≤3 years' duration

Table 5. Expert consensus versus classification systems for selected case profiles*

No.	Skin thickening of the fingers	Fingertips	Telangiectasia	Abnormal nailfold capillaries	Puffy fingers	Raynaud's phenomenon	ILD/ pulmonary fibrosis	PAH	SSc-related autoantibodies	Classified as SSc	Score	1980 ACR criteria fulfilled	No. of experts agreeing (n = 16)
1	Whole finger	Pitting scars	–	Yes	Yes	Yes	–	Yes	Yes	Yes	17	Yes	16
2	Whole finger	Pitting scars	–	–	Yes	Yes	Yes	–	Yes	Yes	15	Yes	16
3	Whole finger	Pitting scars	–	–	Yes	Yes	–	–	Yes	Yes	13	Yes	16
4	Whole finger	Pitting scars	Yes	Yes	–	Yes	–	–	–	Yes	12	Yes	15
5	Whole finger	–	–	Yes	Yes	Yes	–	–	Yes	Yes	12	No	15
6	Whole finger	–	–	Yes	–	Yes	–	–	–	Yes	11	No	10
7	–	Pitting scars	–	–	Yes	Yes	Yes	–	–	Yes	10	?	NA
8	–	Ulcers	–	–	–	Yes	Yes	–	Yes	Yes	10	No	14
9	–	–	–	Yes	–	Yes	Yes	–	Yes	Yes	10	No	NA
10	–	–	–	Yes	Yes	Yes	–	–	Yes	Yes	10	No	NA
11	–	Ulcers	–	–	Yes	Yes	–	–	Yes	Yes	10	No	NA
12	–	–	–	Yes	Yes	Yes	–	–	Yes	Yes	10	No	NA
13	Whole finger	–	–	–	Yes	Yes	–	–	Yes	Yes	10	No	15
14	Whole finger	–	–	–	–	Yes	–	–	Yes	Yes	10	No	NA
15	Whole finger	–	–	Yes	–	Yes	–	–	–	Yes	9	No	NA
16	Whole finger	–	Yes	–	Yes	Yes	–	–	–	Yes	9	No	NA
17	Whole finger	Ulcers	–	–	Yes	Yes	–	–	–	Yes	9	No	NA
18	Whole finger	–	–	Yes	–	Yes	–	–	–	Yes	9	No	NA
19	Whole finger	–	–	Yes	Yes	Yes	–	–	–	Yes	9	No	9
20	Whole finger	–	–	Yes	–	Yes	–	–	–	Yes	9	No	NA
21	–	Pitting scars	–	–	–	Yes	Yes	–	–	No	8	?	NA
22	–	–	–	–	Yes	Yes	–	–	Yes	No	8	No	NA
23	–	Pitting scars	–	Yes	–	Yes	–	–	–	No	8	No	4
24	–	Pitting scars	Yes	–	–	Yes	–	–	–	No	8	No	2
25	–	–	–	Yes	–	Yes	–	–	Yes	No	8	No	NA
26	–	–	–	–	Yes	Yes	Yes	–	–	No	7	No	NA
27	–	–	–	Yes	Yes	Yes	–	–	–	No	7	No	NA
28	Distal to PIP joints	–	–	Yes	Yes	Yes	–	–	–	No	7	No	5
29	–	–	–	Yes	–	Yes	Yes	–	–	No	7	No	NA
30	Whole finger	–	–	–	–	Yes	–	–	–	No	7	No	NA
31	Whole finger	–	Yes	–	Yes	–	–	–	–	No	6	No	NA
32	Distal to PIP joints	–	–	–	–	Yes	–	–	Yes	No	6	No	8
33	–	–	–	–	–	Yes	–	–	Yes	No	6	No	0
34	–	–	–	–	–	–	Yes	–	Yes	No	5	No	NA
35	–	–	–	–	–	Yes	–	Yes	–	No	5	No	0
36	–	–	–	Yes	–	Yes	–	–	–	No	5	No	1
37	–	–	–	Yes	–	–	–	–	Yes	No	5	No	0
38	–	–	–	Yes	–	–	–	–	–	No	2	No	0

* Profiles of 38 cases with likely systemic sclerosis (SSc) or an SSc-like disorder, with presence or absence of the manifestations in the newly developed American College of Rheumatology (ACR)/European League Against Rheumatism SSc classification criteria, are shown. The cases are listed in order of the points awarded using the classification system (Score column) and are classified as SSc if the score is ≥9. For 18 of the cases, the number of experts agreeing that the case had SSc is shown. None of the cases had skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (the single criteria that, if present, immediately classifies the individual as having SSc). Whole finger is sclerodactyly of the entire finger but not proximal to the metacarpophalangeal joints. ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; ? = inconclusive; NA = not applicable (experts were not asked); PIP = proximal interphalangeal.

was similar to the performance in the group overall (Table 4).

The classification system was additionally tested against expert opinion (n = 16 experts), using the set of 38 selected cases (Table 5). All of the cases scoring ≥9 were considered SSc, whereas cases scoring <9 were regarded as not being SSc or were controversial. With the proposed system all of these cases were classified in accordance with consensus-based expert opinion. All cases that were classified as SSc with the 1980 ACR criteria were also classified as SSc with the new criteria, as were several cases not classified as SSc with the 1980 ACR criteria.

Discussion

A classification system for systemic sclerosis is needed to ensure that all patients categorized as having SSc for inclusion in studies do indeed have the disease, based on specific defined characteristics. The major reason to revise the 1980 ACR criteria was that those criteria lacked adequate sensitivity, especially in patients with early SSc or with limited cutaneous SSc (9,10,18). The proposed classification criteria are superior and exhibit greater sensitivity and specificity compared to the 1980 criteria and the classification criteria proposed

by LeRoy and Medsger. All profiles of patients who were considered to have SSc by a majority of experts were indeed classified as SSc with the new classification system, and the new system is more inclusive and also performs well in patients with early disease (≤3 years since diagnosis).

The newly developed classification system includes disease manifestations of the 3 hallmarks of SSc: fibrosis of the skin and/or internal organs, production of certain autoantibodies, and vasculopathy. The 4 items comprising the 1980 ACR classification criteria (scleroderma proximal to the metacarpophalangeal joints, sclerodactyly, digital pitting scars [not pulp loss], and bilateral basilar pulmonary fibrosis) (3) are also included, as are the items in the criteria proposed in 2001 by LeRoy and Medsger (Raynaud's phenomenon, autoantibodies, nailfold capillaroscopy abnormalities, skin fibrosis) (6).

The new criteria include 1 criterion that alone is sufficient for classification as SSc: skin thickening of the fingers extending proximal to the metacarpophalangeal joints, which is similar to the 1980 criteria. If the single sufficient criterion is not fulfilled, the point system is applied and patients with a score of ≥9 are classified as having SSc. All items in the classification criteria represent measurements that are performed in routine clinical practice. The criteria are meant for inclusion of SSc patients in studies, not for SSc diagnosis. Although the list of items in the classification criteria mimics the list of items one usually uses for diagnosis, in practice the diagnosis of SSc may also be informed by items not included in the classification criteria, such as tendon friction rubs, calcinosis, and dysphagia. Consequently, patients *classified* as having SSc are a subset of patients being *diagnosed* as having SSc, with diagnosis being more sensitive. Ideally, there would be no difference between diagnosis and classification criteria.

As intended, the new classification system incorporates the considerable advances made in the diagnosis of SSc. It includes the concept of specific serum autoantibodies such as anti–topoisomerase I, anticentromere, and anti–RNA polymerase III (15,23). There is the possibility that testing for additional SSc autoantibodies, such as anti-Th/To, anti–U3 RNP, and others, may become more widely available. The criteria also acknowledge the value of magnified nailfold visualization in the diagnosis of SSc (14,15). Although capillaroscopy can be performed with highly specialized equipment such as videocapillaroscopy cameras, simple in-office ophthalmoscopes or dermatoscopes suffice for distinguishing between normal and abnormal nailfold capillaries (24,25). Capillaroscopy is now widely used, and considering the value of magnified nailfold visualization in the diagnosis and management of SSc, these new criteria may encourage acquisition of this skill by physicians caring for SSc patients. Likewise, criteria for pulmonary artery hypertension have changed over the years. The ACR/EULAR committee recognizes this, and the diagnosis of pulmonary artery hypertension should be based on the most recent accepted criteria from right-sided heart catheterization.

Several items that are useful for recognizing SSc in clinical practice, such as calcinosis, flexion contractures of the fingers, tendon or bursal friction rubs, renal crisis, esophageal dilatation, and dysphagia are not included in the criteria. These were considered but did not substantially improve sensitivity or specificity. For example, renal crisis is a strong indicator of SSc, but its low frequency of occurrence makes it less useful for the purpose of classification (20). The committee considered a non–point-based additive system (8), such as the ACR systemic lupus erythematosus criteria (26) or the 1980 ACR SSc criteria. We concluded, however, that assigning weights yielded superior results for SSc classification. Indeed, the weights were simplified to single-digit numbers to make the system easy to use even in the absence of a computing device. Similar weighted systems have been used for other rheumatic diseases (27). The committee also decided not to include "probable" or "possible" SSc in the classification.

Examples of profiles not captured by the 1980 ACR criteria that fulfilled the new classification criteria are combinations of skin thickening of the whole finger, SSc-related autoantibodies, and pulmonary arterial hypertension and/or Raynaud's phenomenon. A patient with Raynaud's phenomenon, autoantibodies, and abnormal nailfold capillaries is not classified as having SSc, although such a patient may develop SSc over subsequent years (6,15).

Patients may have disease manifestations similar to those of SSc that are better explained by another well-defined disorder, such as nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, porphyria, lichen sclerosis, graft-versus-host disease, or diabetic cheiroarthropathy. We decided it was not necessary to develop criteria that differentiated SSc specifically from these conditions. Patients with some of these diseases were included in the validation cohort of patients with SSc-like disorders, and it is possible that specificity may have been slightly higher had they been excluded.

In developing the revised SSc classification crite-

ria, we followed the recommendations and guidelines of the ACR and EULAR, which included 1) collaboration between clinical experts and clinical epidemiologists in criteria development, 2) evaluation of the psychometric properties of each candidate criterion, and 3) description of the test sample (origin of the patients and control subjects) (7,28). Ideally, phases of criteria development should have a balance between expert opinion and data-driven methods; yet, there should be avoidance of circularity of reasoning (a bias that can occur when the same experts developing the criteria are the ones contributing cases and comparison patients) (29). We included different experts at different steps in the development of the SSc criteria, to avoid circularity.

Testing and validating a classification system for SSc is difficult because there is no gold standard for defining a particular case as SSc; that is, there is no incontrovertible test or criterion. We relied on expert opinion for our gold standard, which is similar to the process used in the development of other criteria (8).

In the absence of a gold standard, we developed and tested the proposed classification system against two standards of expert opinion: 1) the opinion of the clinician who selected cases for the North American and European derivation and validation cohorts, and 2) the combined opinion of a group of clinical experts in SSc. Both standards have strengths and weaknesses. Each individual clinician who selected cases had access to information that could have included aspects not captured by the forms, which were restricted to 23 particular manifestations. Data were obtained from several sites in Europe and North America, so this should improve generalizability and reduce selection bias. However, it is possible that other expert clinicians may have had a different opinion about particular cases. The consensus opinion of a group of experts who had the opportunity to discuss controversial cases strengthens the combined expert opinion. However, the group may not have been aware of some relevant information not included in the available data. It is also difficult for a group of experts to consider hundreds of cases in depth; however, this was managed by having the group consider in depth only those cases, or combinations of items, that appeared to be controversial. In this way, the expert group was able to form a consensus over the whole range of cases in the database. A key strength of the present work is the use of both standards for testing and validation of the proposed system.

The approach we used has other strengths and limitations as well. The methodology was state of the art, with validation by data and by expert opinion at every step. Various methods used in the development process have already been described (19,20). The criteria have face validity, because the items are routinely assessed in daily clinical practice and also were included in other important SSc classification criteria sets. The criteria allow for new developments in e.g., autoantibody testing availability and/or new identification of scleroderma-associated autoantibodies, or assessment of nailfold capillaries. Formal conjoint analysis to derive the weights associated with items improved the sensitivity and specificity of the items, as was found also in the development of the recent ACR/EULAR criteria for the classification of rheumatoid arthritis (30).

The criteria have not been validated in ethnic groups that are not common in North America and Europe. This will require further studies. Regarding clinical use, the number of items and weights may not be easy to remember, but wide availability and (electronic) applications can be developed. The SSc classification criteria steering committee and the expert consultants agreed that the criteria could allow for classification of patients with another rheumatic disease as also having SSc (e.g., having both systemic lupus erythematosus and SSc, or rheumatoid arthritis and SSc, etc.). Although this is a possible limitation, it permits individual researchers to decide whether to include subjects who fulfill criteria for more than one rheumatic disease in any particular study.

Conclusions

The ACR/EULAR classification criteria for SSc perform better than 1980 ACR preliminary criteria in terms of both sensitivity and specificity. They are relatively simple to apply to individual subjects. These criteria may be endorsed as inclusion criteria for SSc studies. Validation in other populations is encouraged.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Van den Hoogen and Pope had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Vasculitis

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ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 10, October 2015, pp 2569–2580
DOI 10.1002/art.39333
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SPECIAL ARTICLE

2015 Recommendations for the Management of Polymyalgia Rheumatica

A European League Against Rheumatism/American College of Rheumatology Collaborative Initiative

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This article is published simultaneously in the October 2015 issue of *Annals of the Rheumatic Diseases*.

Supported by research grants from the American College of Rheumatology and the European League Against Rheumatism.

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Abstract. **Therapy for polymyalgia rheumatica (PMR) varies widely in clinical practice as international recommendations for PMR treatment are not currently available. In this paper, we report the 2015 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) recommendations for the management of PMR. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology as a framework for the project. Accordingly, the direction and strength of the recommendations are based on the quality of evidence, the balance between desirable and undesirable effects, patients' and clinicians' values and preferences, and resource use. Eight overarching principles and nine specific recommendations were developed covering several aspects of PMR, including basic and follow-up investigations of patients under treatment, risk factor assessment, medical access for patients and specialist referral, treatment strategies such as initial glucocorticoid (GC) doses and subsequent tapering regimens, use of intramuscular GCs and disease modifying anti-rheumatic drugs (DMARDs), as well as the roles of non-steroidal anti-rheumatic drugs and non-pharmacological interventions. These recommendations will inform primary, secondary and tertiary care physicians about an international consensus on the management of PMR. These recommendations should serve to inform clinicians about best practices in the care of patients with PMR.**

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Dr. Dejaco has received consulting fees, speaking fees, and/or honoraria from Bristol-Myers Squibb, Pfizer, AbbVie, MSD, Merck Serono, and Roche, and research funding from Pfizer and MSD. Dr. Mackie has received consulting fees, speaking fees, and/or honoraria from Pfizer, Napp Pharmaceuticals, and AstraZeneca. Dr. Bachta has received consulting fees, speaking fees, and/or honoraria from Medac, Abbott, ENEL-MED, Wyeth, and Lilly, and research funding from Wyeth and Lilly. Dr. Balint has received consulting fees, speaking fees, and/or honoraria from Pfizer, SonoSite, and Abbott, and research funding from Abbott and Bristol-Myers Squibb. Dr. Buttgereit has received consulting fees, speaking fees, and/or honoraria from Merck Serono, Horizon Pharma, and Mundipharma, and research funding from Merck Serono and Horizon Pharma. Dr. Carsons has received consulting fees, speaking fees, and/or honoraria from Centocor. Dr. Cid has received consulting fees, speaking fees, and/or honoraria from Centocor, Roche, and Bristol-Myers Squibb. Dr. Cimmino has received consulting fees, speaking fees, and/or honoraria from Roche, Bristol-Myers Squibb, and Menarini, and research funding from Roche. Dr. Duftner has received consulting fees, speaking fees, and/or honoraria from Bristol-Myers Squibb, Pfizer, AbbVie, MSD, Merck Serono, and Roche. Dr. Jayne has received consulting fees, speaking fees, and/or honoraria from Roche/Genentech, and research funding from the company. Dr. Maharaj has received consulting fees, speaking fees, and/or honoraria from AstraZeneca and Pfizer. Dr. Martinez-Taboada has received consulting fees, speaking fees, and/or honoraria from UCB Pharma, Pfizer, Cellerix, and Abbott, and research funding from Roche. Dr. Mori has received research funding from Bristol-Myers Squibb. Dr. Salvarani has received consulting fees, speaking fees, and/or honoraria from Novartis. Dr. Schirmer has received consulting fees, speaking fees, and/or honoraria from Abbott, Pfizer, Amgen, GlaxoSmithKline, and MSD. Dr. Schmidt has received consulting fees, speaking fees, and/or honoraria from Berlin-Chemie, Medac, Pfizer, AbbVie, Roche, Mundipharma, UCB, and MSD, and research funding from Mundipharma, Novartis, MJD Pharmaceutical, Actelion, General Electric, Esadie, and Savient. Dr. Spiera has received research funding from Roche/Genentech. Dr. Matteson has received research funding from Ardea, Sanofi, Centocor/Janssen, Celgene, Amgen, Roche, Genentech, Mesoblast, Novartis, Pfizer, and UCB Pharma. Dr. Dasgupta has received consulting fees, speaking fees, and/or honoraria from Merck and research funding from Roche, Mundipharma, and Servier.

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Submitted for publication February 20, 2015; accepted in revised form July 13, 2015.

Introduction

There are wide variations in the treatment of polymyalgia rheumatica (PMR) with respect to glucocorticoid (GC) dosages, tapering strategies, use of disease modifying anti-rheumatic drugs (DMARDs) and duration of treatment. Up to 29–45% of patients with PMR do not adequately respond to GCs within 3–4 weeks. Relapses and long-term GC dependency are common (1–4). GC side effects are frequently observed, occurring in around 50% of patients, and present a further challenge (5,6). Well considered, international recommendations can serve to standardize practice and improve patient care.

Primary objective of the recommendations. These recommendations are intended for the management of patients with PMR in various settings and are based on clinical evidence and expert opinion including informed patient decision-making.

Target population. The target population are patients with PMR based on clinician diagnosis which may be supported by currently available diagnostic or classification criteria (3,4,7–11). Management of PMR with concomitant giant cell arteritis (GCA), rheumatoid arthritis (RA) or other conditions that present with PMR features or mimic PMR is not addressed by these recommendations.

Target users. The target users of these recommendations are primary, secondary and tertiary care physicians (that is, general practitioners [GPs], specialists in general [internal] medicine and rheumatologists).

Methods

For a detailed description of methods, see online supplementary file S1, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39333/abstract.

In brief, we used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology as a framework (12–15). We formulated 12 PICO (problem/population, intervention, comparison, and outcome) questions on interventions and 10 questions on prognostic factors (see online supplementary box S1A and S1B [http://onlinelibrary.wiley.com/doi/10.1002/art.39333/abstract], or the accompanying paper by Dejaco et al [16]). The systematic literature review (SLR) was conducted by two investigators (CDe and YPS) using Ovid MEDLINE, Embase, PubMed, CINAHL, Web of Science and the Cochrane Library databases (from January 1970 until April 2014), and applying the thesauri of PMR, text words, abbreviations and truncated text words. Outcome parameters used in the SLR may be found in supplementary box S2 (http://onlinelibrary.wiley.com/doi/10.1002/art.39333/abstract). Quality appraisal of interventional and prognostic studies was performed using GRADE (17,18) and the Quality in Prognostic Studies (QUIPS) tool (19), respectively. According to GRADE methodology, a guideline panel should consider the following aspects when formulating recommendations: 1) overall quality of evidence; 2) balance between desirable and undesirable effects; 3) patients' and clinicians' values and preferences; and 4) resource use. External evidence (from other American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] recommendations; see online supplementary table S1 [http://onlinelibrary.wiley.com/doi/10.1002/art.39333/abstract] for details) on safety aspects related to the use of nonsteroidal anti-inflammatory drugs (NSAIDs), GCs and methotrexate (MTX) was taken into account as indirect evidence, in order to identify the optimal trade-off between the benefit and harm of interventions. Prognostic factors were used to build subgroups and to adapt the recommendations based on the presence or absence of unfavorable prognostic factors. Final recommendations were either "in favor" or "against" an intervention, and were graded as "conditional" or "strong." A strong recommendation in favor (against) was considered when the panel was certain that benefits did (did not) outweigh risks and burdens, the preferences/values of patients were met (not met) and resource use was reasonable (unreasonably high). If uncertainty existed, a conditional recommendation was made.

Results

The results of the SLR are reported in a separate manuscript (16). See online supplementary file S2 (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39333/abstract) for a summary of the SLR and external evidence considered by the guideline panel.

General aspects. These recommendations should be understood as clinical advice and do not dictate the care of a particular patient. The EULAR and ACR consider adherence to these recommendations to be voluntary, with the physician making the ultimate decision to apply them in light of each patient's individual circumstances.

Overarching principles for the management of PMR. The group agreed upon several principles deemed to be fundamental aspects of clinical care in PMR as detailed in Box 1. These principles have not directly resulted from the SLR, but are consensus based. They are intended as a framework for the implementation of

Box 1. Summary of the 2015 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) recommendations for the management of polymyalgia rheumatica (PMR)

Target population:
Patients with PMR based on clinician diagnosis which may be supported by currently available diagnostic or classification criteria (3,4,7–11).
Overarching principles for the management of PMR:

A. Adoption of a safe and specific approach to ascertain the PMR case definition. The clinical evaluation should be directed toward exclusion of relevant mimicking (eg, non-inflammatory, inflammatory (such as giant cell arteritis or rheumatoid arthritis), drug-induced, endocrine, infective and neoplastic) conditions.
B. Every case of PMR should have the following assessments prior to the prescription of therapy (primary or secondary care):
   - ▶ Documentation of a basic laboratory dataset. This will help to exclude mimicking conditions and establish a baseline for monitoring of therapy. This should include rheumatoid factor and/or anti–cyclic citrullinated peptide antibodies (ACPA), C-reactive protein and/or erythrocyte sedimentation rate (ESR), blood count, glucose, creatinine, liver function tests, bone profile (including calcium, alkaline phosphatase) and dipstick urinalysis. Additional investigations to consider are protein electrophoresis, thyroid stimulating hormone (TSH), creatine kinase and vitamin D.
   - ▶ Depending on clinical signs and symptoms and the likelihood of the alternative diagnoses, additional more extensive serological tests such as anti-nuclear antibodies (ANA), anti–cytoplasmic neutrophil antibodies (ANCA) or tuberculosis tests may be performed to exclude mimicking conditions. Additional investigations such as chest radiographs may be considered at the discretion of the physician in order to exclude other diagnoses.
   - ▶ Determination of comorbidities (particularly hypertension, diabetes, glucose intolerance, cardiovascular disease, dyslipidemia, peptic ulcer, osteoporosis [and particularly recent fractures]), presence of cataract or (risk factors for) glaucoma, presence of chronic or recurrent infections, and co-medication with non-steroidal anti-inflammatory drugs (NSAIDs) as outlined in Smolen et al (21) and Gossec et al (22), other relevant medications and risk factors for steroid-related side effects. Female sex was associated with a higher risk of glucocorticoid (GC) side effects in low to moderate quality studies (23–25).
   - ▶ The role of risk factors for relapse/prolonged therapy is not clear yet. Baseline factors that were associated in low to moderate quality studies with a higher relapse rate and/or prolonged therapy in PMR studies were: female sex (24,26), high ESR (>40 mm/hour) (26–31) and peripheral inflammatory arthritis (32). A number of equally low to moderate quality studies, however, failed to demonstrate an association between these factors and relapse/prolonged therapy (27–30,32–44).
C. Consideration of specialist referral, particularly in case of atypical presentation (such as peripheral inflammatory arthritis, systemic symptoms, low inflammatory markers, age <60 years), experience of or high risk of therapy-related side effects, PMR refractory to GC therapy, and/or relapses/prolonged therapy.
D. Treatment of PMR patients should aim at the best care and must be based on a shared decision between the patient and the treating physician.
E. Patients should have an individualized PMR management plan. Patient perspective and preferences should be considered in the individualized choice of initial GC dose and subsequent tapering of GCs in PMR.
F. Patients should have access to education focusing on the impact of PMR and treatment (including comorbidities and disease predictors) and advice on individually tailored exercise programs.
G. Every patient treated for PMR in primary or secondary care should be monitored with the following assessments: risk factors and evidence for steroid-related side effects, comorbidities, other relevant medications, evidence and risk factors for relapse/prolonged therapy. Continuous documentation of a minimal clinical and laboratory dataset should be conducted while prescribing GCs. Follow-up visits are suggested every 4–8 weeks in the first year, every 8–12 weeks in the second year, and as indicated in case of relapse or as prednisone is tapered and discontinued.
H. It is important for patients to have rapid and direct access to advice from doctors, nurses or trained allied healthcare staff to report any changes in their condition such as flares and adverse events.

Specific recommendations for the management of PMR patients:

1. The panel strongly recommends using GC instead of NSAIDs in patients with PMR, with the exception of possible short-term use of NSAIDs and/or analgesics in PMR patients with pain related to other conditions. No specific recommendation can be made for analgesics.
2. The panel strongly recommends using the minimum effective individualized duration of GC therapy in PMR patients.
3. The panel conditionally recommends using the minimum effective GC dose within a range of 12.5–25 mg prednisone equivalent daily as the initial treatment of PMR. A higher initial prednisone dose within this range may be considered in patients with a high risk of relapse and low risk of adverse events, whereas in patients with relevant comorbidities (eg, diabetes, osteoporosis, glaucoma, etc.) and other risk factors for GC-related side effects, a lower dose may be preferred. The panel discourages conditionally the use of initial doses ≤7.5 mg/day and strongly recommends against the use of initial doses >30 mg/day.
4. The panel strongly recommends individualizing dose tapering schedules, predicated to regular monitoring of patient disease activity, laboratory markers and adverse events.The following principles of GC dose tapering are suggested:
   A. Initial tapering: Taper dose to an oral dose of 10 mg/day prednisone equivalent within 4–8 weeks.
   B. Relapse therapy: Increase oral prednisone to the pre-relapse dose and decrease it gradually (within 4–8 weeks) to the dose at which the relapse occurred.
   C. Tapering once remission is achieved (following initial and relapse therapies): Taper daily oral prednisone by 1 mg every 4 weeks (or by 1.25 mg decrements using schedules such as 10/7.5 mg alternate days, etc.) until discontinuation given that remission is maintained.
5. The panel conditionally recommends considering intramuscular (i.m.) methylprednisolone as an alternative to oral GCs. The choice between oral GCs and i.m. methylprednisolone remains at the discretion of the treating physician. In one clinical trial, a starting dose of 120 mg methylprednisolone i.m. injection every 3 weeks was applied (23).
6. The panel conditionally recommends using a single rather than divided daily doses of oral GCs for the treatment of PMR, except for special situations such as prominent night pain while tapering GCs below the low-dose range (prednisone or equivalent <5 mg daily).
7. The panel conditionally recommends considering early introduction of methotrexate (MTX) in addition to GCs, particularly in patients at a high risk for relapse and/or prolonged therapy as well as in cases with risk factors, comorbidities and/or concomitant medications where GC-related adverse events are more likely to occur. MTX may also be considered during follow-up of patients with a relapse, without significant response to GC or experiencing GC-related adverse events. MTX has been used at oral doses of 7.5–10 mg/week in clinical trials (24–27).
8. The panel strongly recommends against the use of TNFα blocking agents for treatment of PMR.
9. The panel conditionally recommends considering an individualized exercise program for PMR patients aimed at the maintenance of muscle mass and function, and reducing risk of falls especially in older persons on long-term GCs as well as in frail patients.
10. The panel strongly recommends against the use of the Chinese herbal preparations Yanghe and Biqi capsules in PMR patients.

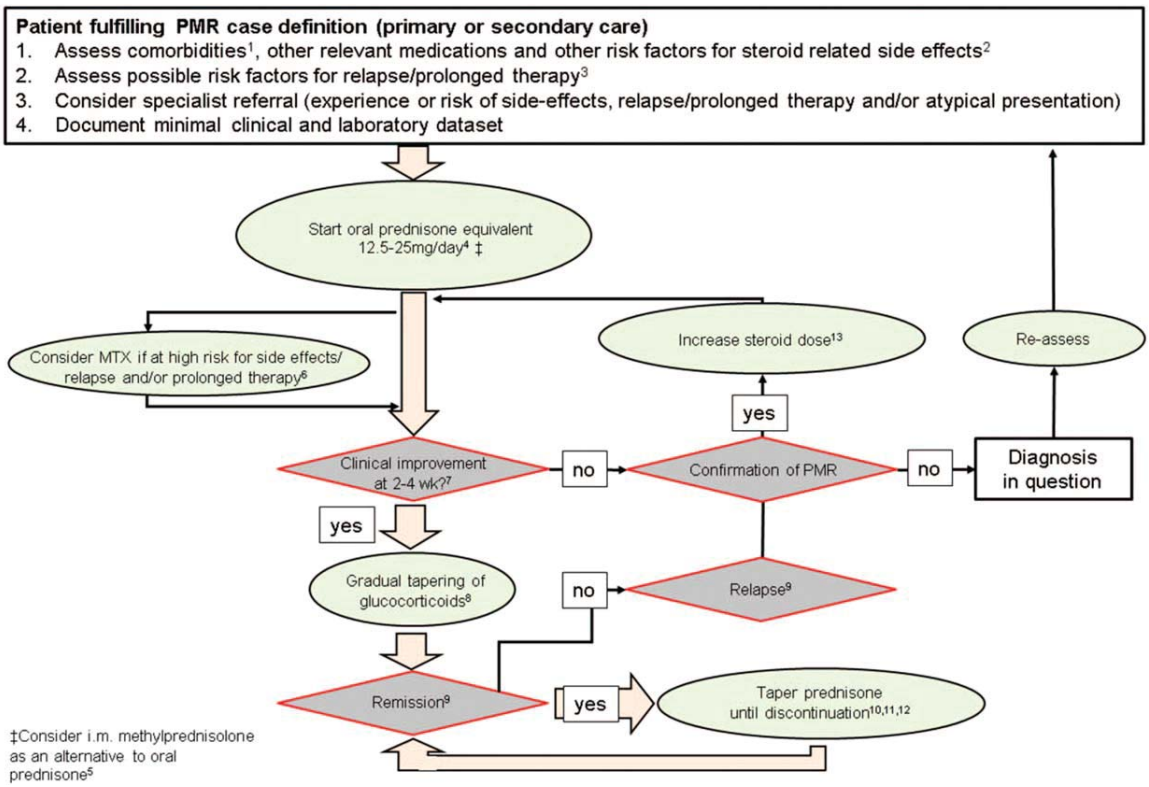
Patient fulfilling PMR case definition (primary or secondary care)
1. Assess comorbidities[1], other relevant medications and other risk factors for steroid related side effects[2]
2. Assess possible risk factors for relapse/prolonged therapy[3]
3. Consider specialist referral (experience or risk of side-effects, relapse/prolonged therapy and/or atypical presentation)
4. Document minimal clinical and laboratory dataset
Start oral prednisone equivalent 12.5-25mg/day[4] ‡
Consider MTX if at high risk for side effects/ relapse and/or prolonged therapy[6]
Increase steroid dose[13]
Re-assess
yes
Clinical improvement at 2-4 wk?[7]
no
Confirmation of PMR
no
Diagnosis in question
yes
Gradual tapering of glucocorticoids[8]
no
Relapse[9]
Remission[9]
yes
Taper prednisone until discontinuation[10,11,12]
‡Consider i.m. methylprednisolone as an alternative to oral prednisone[5]

Figure 1. Algorithm based on the 2015 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) recommendations for the management of polymyalgia rheumatica (PMR). The algorithm is applied to patients with PMR based on clinician diagnosis which may be supported by currently available diagnostic or classification criteria (3,4,7–11). The algorithm assumes the consideration of overarching principles emphasizing the importance of assessing comorbidities, other relevant medications and possible risk factors for steroid-related side effects and relapse/prolonged therapy. In addition, patients diagnosed in primary care should be considered for specialist referral, particularly in case of atypical presentation (such as peripheral inflammatory arthritis, systemic symptoms, low inflammatory markers, age <60 years), experience or high risk of therapy-related side effects and/or relapse/prolonged therapy. A minimal clinical and laboratory dataset should be documented in each patient before prescribing therapy. [1]Examples for comorbidities associated with an increased risk of glucocorticoid (GC)–related side effects are (according to Duru et al [32] and Hoes et al [35]): hypertension, diabetes, glucose intolerance, cardiovascular disease, dyslipidemia, peptic ulcer, osteoporosis (and particularly recent fractures), presence of cataract or (risk factors for) glaucoma, presence of chronic or recurrent infections, and co-medication with NSAIDs. [2]A baseline factor that was associated with a higher risk of GC-related adverse events in PMR studies was: female sex (37–39). [3]The role of risk factors for relapse/prolonged therapy is not yet clear. Baseline factors that were associated with a higher relapse rate and/or prolonged therapy in PMR studies were: female sex (38,47), high erythrocyte sedimentation rate (ESR) (>40 mm/hour) (47–51,53) and peripheral inflammatory arthritis (54). A number of studies, however, failed to demonstrate association between these factors and relapse (48–51,54,67–78). [4]Use the minimum effective dose out of a range of 12.5–25 mg prednisone equivalent daily: a high risk of relapse/prolonged therapy favors a higher dose, while a high risk of side effects favors a lower dose. [5]In one randomized controlled trial, 120 mg methylprednisolone intramuscular (i.m.) injection was used every 3 weeks as a starting dose (23). I.m. methylprednisolone may not be available in all countries and the possible long-term benefit in terms of efficacy and GC-sparing effects of this preparation is unknown. [6]Methotrexate (MTX) has been used at oral doses of 7.5–10 mg/week in clinical trials (24–27). [7]Clinical improvement should be noted after 2 weeks, and almost complete response can be expected after 4 weeks. The definition of response criteria was beyond the scope of this project; however, a definition of response was proposed in Dasgupta et al (3,4) [8]For initial GC tapering, we recommend reducing the oral dose gradually to a dose of 10 mg/day prednisone equivalent within 4–8 weeks; after relapse therapy the dose should be decreased gradually (within 4–8 weeks) to the dose at which the relapse occurred. For i.m. methylprednisolone, a dose of 120 mg every 3 weeks was used for the first 9 weeks in Dasgupta et al (23). No recommendation about dose adjustments of MTX can be made. [9]The definition of criteria for remission and relapse was beyond the scope of this project. Definitions of remission and relapse used in clinical studies are summarized in Dejaco et al (65). [10]Once remission is achieved (following initial and relapse therapies), taper oral prednisone by 1 mg/4 weeks (or similar, eg, 2.5 mg/10 weeks) until discontinuation given that remission is maintained. In case i.m. methylprednisolone is used, the following tapering regimen was previously applied (23): 100 mg methylprednisolone i.m. at week 12, then continuation of the injections at monthly intervals with the dose reduced by 20 mg every 12 weeks until week 48. Thereafter, the dose was reduced by 20 mg every 16 weeks until discontinuation. [11]The group suggests that PMR patients be followed up every 4–8 weeks in the first year, every 8–12 weeks in the second year and as indicated in case of relapse or as prednisone is tapered off. [12]No recommendation can be made for minimal/optimal duration of therapy. In case patients are treated with a combination of GCs plus MTX and GCs have been withdrawn already, discontinuation of MTX may be considered. [13]Initial lack of response (eg, insufficient improvement of symptoms within 2 weeks): increase oral dose up to 25 mg prednisone equivalent. In case i.m. methylprednisolone is used, consider switching to oral GCs. Relapse therapy: increase dose to the previously effective (ie, pre-relapse) dose.

the specific treatment recommendations and are of a general "overarching" nature, a concept adapted from earlier EULAR recommendations (20–22).

Specific recommendations. See Box 1 for a summary of the recommendations. A flow-chart for the management of PMR patients is depicted in Figure 1.

Recommendation 1: (PICO 1) The panel strongly recommends using GCs instead of NSAIDs in patients with PMR, with the exception of possible short-term use of NSAIDs and/or analgesics in PMR patients with pain related to other conditions (eg, co-existing osteoarthritis). No specific recommendation can be made for analgesics.

Explanation: The group recommends strongly against the use of NSAIDs compared to GCs in the treatment of PMR since the relative harm of long-term NSAID use (as mainly indicated by external evidence) outweighs the possible small benefits in PMR. No specific recommendation can be made for analgesics. On a basis of consensus, the panel recognized that the short-term use of NSAIDs and/or analgesics may be necessary in the setting of pain related to conditions other than PMR.

Recommendation 2: (PICO 2) The panel strongly recommends using the minimum effective individualized duration of GC therapy in PMR patients.

A more specific recommendation is not possible due to the lack of published evidence on this issue. On a basis of consensus and in accordance with the overarching principles, the group unanimously agreed to choose the minimum effective individualized duration and dose of GCs to balance benefit versus harm after assessing risk factors for GC-related adverse events, comorbidities, concomitant medications, relapses and prolonged therapy. Our recommended GC tapering schedule (see Recommendation 4) assumes a minimum of 12 months of treatment. A more specific statement is not possible because of the lack of PMR studies on this particular topic and because of the multiple subgroups and factors that need to be taken into account.

Recommendation 3: (PICOs 3–5) The panel conditionally recommends using the minimum effective GC dose within a range of 12.5–25 mg prednisone equivalent daily as the initial treatment of PMR. A higher initial prednisone dose within this range may be considered in patients with a high risk of relapse and low risk of adverse events, whereas in patients with relevant comorbidities (eg, diabetes, osteoporosis, glaucoma, etc.) and other risk factors for GC-related side effects, a lower dose may be preferred. The panel discourages conditionally the use of initial doses $\leq$7.5 mg/day and strongly recommends against the use of initial doses $>$30 mg/day.

According to the SLR on prognostic factors and based on clinical experience, the group agreed upon the existence of various PMR subgroups that are characterized by different risks of relapse, prolonged GC therapy and/or GC-related adverse events as well as by various comorbidities and co-medications. As there are insufficient data to make evidence-based recommendations for all conceivable subgroups, and taking current clinical practice into account (28–30), the panel agreed upon the use of the minimum effective GC dose out of a range of 12.5–25 mg prednisone equivalent daily balancing benefits versus harms. The panel did not construct case vignettes as a possible aid for clinical practice; however, it is suggested that a higher initial prednisone dose (within the given range) may be used in patients with a high risk of relapse and low risk of adverse events, whereas in patients with relevant comorbidities (eg, diabetes, osteoporosis, glaucoma, etc.) and other risk factors for GC-related side effects, a lower dose may be preferred.

The group conditionally discourages low ($\leq$7.5 mg/day) and strongly recommends against high ($>$30 mg/day prednisone equivalent) initial GC doses. For this statement the group extrapolated the data from randomized controlled trials (29,31), and took clinical experience, national PMR guidelines (28–30), as well as current ACR and/or EULAR recommendations on the use of GCs in rheumatic diseases into account (32–35). In addition, there is incontrovertible external evidence of harm from long-term large doses of GCs (32–35) and lack of evidence for any benefit of a high-dose regimen in PMR. It was unanimously agreed among the group that patients requiring high doses of GCs should be evaluated for alternate diagnoses and an alternate management plan.

Recommendation 4: (PICO 6) The panel strongly recommends individualizing dose-tapering schedules, based on regular monitoring of patient disease activity, laboratory markers and adverse events.

The following principles of GC dose tapering are suggested:

A. Initial tapering: Taper dose to an oral dose of 10 mg/day prednisone equivalent within 4–8 weeks.
B. Relapse therapy: Increase oral prednisone to the pre-relapse dose and decrease it gradually (within 4–8 weeks) to the dose at which the relapse occurred.
C. Tapering once remission is achieved (following initial and relapse therapies): Taper daily oral prednisone by 1 mg every 4 weeks (or by 1.25 mg decrements using schedules such as 10/7.5 mg on alternate days, etc.) until discontinuation as long as remission is maintained.

In accordance with the overarching principles, the panel agreed upon a strong recommendation to

individualize dose tapering and to regularly monitor PMR patients. Further, the panel proposed general principles for initial and post-relapse tapering of GCs (based on consensus and current clinical practice) but did not fix a schedule as in other guidelines (28–30). The panel agreed that equivalent objectives may be achieved by alternative tapering schedules. For example, a patient with a high initial prednisone dose (eg, 25 mg/day) may have a fast initial taper followed by a more gradual decrease in the GC dose, whereas in a patient starting at a lower initial dose (eg, 12.5 mg/day), the initial dose may be kept constant for longer and then eventually reduced.

The group suggested prednisone should be tapered by 1 mg/4 weeks or similar once remission is achieved. Again, the panel emphasized the important overall principle of gradual GC reduction without the need to prescribe a fixed schedule. The group further recognized that 1 mg prednisone tablets are not available in all countries (making a reduction of 1 mg/4 weeks unfeasible) and that other regimens such as alternate day reductions (eg, 10/7.5 mg on alternate days, etc.) are common clinical practice (28).

Recommendation 5: (PICO 7) The panel conditionally recommends considering intramuscular (i.m.) methylprednisolone as an alternative to oral GCs. The choice between oral GCs and i.m. methylprednisolone remains at the discretion of the treating physician.

In one clinical trial, i.m. methylprednisolone was applied at a dose of 120 mg every 3 weeks until week 9. At week 12, 100 mg were used and subsequently, injections were continued at monthly intervals and the dose was reduced by 20 mg every 12 weeks until week 48. Thereafter, the dose was reduced by 20 mg every 16 weeks until discontinuation (23,36).

The panel did not specify a clinical phenotype where i.m. GCs would be appropriate or adequate therapy; however, the panel agreed that in clinical practice this preparation may be considered in cases where a lower cumulative GC dose is desirable, for example in female patients with difficult to control hypertension, diabetes, osteoporosis and/or glaucoma (37–39). Nonetheless, the panel acknowledged that there is a lack of convincing evidence showing significantly fewer side effects with i.m. methylprednisolone than with oral GC therapy.

The reasons why the panel did not endorse a strong recommendation for the use of i.m. methylprednisolone are the following: 1) the efficacy of i.m. methylprednisolone is supported by a single randomized controlled trial and confirmation of these data is still necessary (23,36); 2) this trial was neither designed nor powered as a non-inferiority trial and therefore, a difference between the efficacy of i.m. and oral GC cannot be excluded; 3) the trial failed to demonstrate a reduction in GC-related adverse events except for weight gain; 4) the long-term benefit of this preparation is unknown (particularly with respect to a possible reduction in GC side effects); and 5) i.m. methylprednisolone is not available in all countries.

Recommendation 6: (PICO 8) The panel conditionally recommends using a single rather than divided daily doses of oral GCs for the treatment of PMR, except for special situations such as prominent night pain while tapering GCs below the low-dose range (prednisone or equivalent <5 mg daily).

There are no studies available addressing this issue specifically in PMR. Based on clinical experience and because of the concern that adverse events (including disturbance of the hypothalamic–pituitary–adrenal axis) may be higher with divided doses, the group agreed against the general use of divided GC doses in PMR (40–43). The effectiveness and acceptability of a single daily GC dose has been standard clinical practice in PMR and other inflammatory conditions (44,45) and evening doses can cause circadian rhythm and sleep disturbances (46).

In special situations such as in case of night pain while tapering below the low-dose range (prednisone or equivalent <5 mg daily), split doses may be considered. However, persistent breakthrough symptoms should prompt re-consideration of the diagnosis.

Recommendation 7: (PICO 9) The panel conditionally recommends considering early introduction of MTX in addition to GCs, particularly in patients at high risk of relapse and/or prolonged therapy as well as in cases with risk factors, comorbidities and/or concomitant medications where GC-related adverse events are more likely to occur. MTX may also be considered during follow-up in patients with a relapse, without a significant response to GC or experiencing GC-related adverse events.

In clinical trials, MTX has been used at oral doses of 7.5–10 mg/week (24–27).

Similar to the explanation of Recommendation 5, the panel felt that there is no clinical prototype unconditionally warranting treatment with MTX, rather the use of this drug should be discussed on an individual basis. In clinical practice, MTX may be considered for example in female patients (36,39,47) with high initial erythrocyte sedimentation rate (ESR) (>40 mm/hour) (48–53), peripheral inflammatory arthritis (54) and/or comorbidities that may be exacerbated by GC therapy.

The panel also reached a consensus that MTX should be considered in patients who have relapsed (either on or off GCs), cases without significant response

Box 2. Research agenda

The group agreed that future studies in polymyalgia rheumatica (PMR) should be multicenter and properly powered using an agreed, validated core outcome set and a robust trial design that would maximize the power of studies, facilitate regulatory approvals and allow future meta-analysis.

Specific research questions:

1. Which outcome measures including patient-related outcomes, and response, remission and relapse criteria should be used in PMR? What is the value of a composite score? What are the most relevant treatment targets in PMR?
2. **What is the efficacy and safety of different routes of glucocorticoid (GC) administration (oral, intramuscular, intra-articular), different initial GC doses, various GC tapering regimens, and different GC flare doses?**
3. **What is the efficacy and safety of DMARDs (non-TNFα biologic, conventional synthetic and conventional targeted) in PMR? What is the optimal strategy for using DMARDs in PMR: monotherapy versus combination therapy, early versus late introduction, and (particularly for biologics) use with or without GCs?**
4. What is the minimal/optimal duration of therapy and which strategies for withdrawing GCs and/or DMARDs yield the best efficacy/safety profile?
5. **What is the optimal strategy for shared primary and specialty care including recommendations for specialist referral? How can patients be better involved in treatment decisions, and are there any decision aids? What is the role of self-management?**
6. What is the value of tight control (ie, treat to target) versus conventional management strategies in PMR?
7. **How should patients with long-standing disease and long-term low-dose GC therapy be managed?**
8. What is the cost utility and effectiveness of DMARD use in PMR (versus GC use alone)?
9. What is the value of non-pharmacological therapies in PMR? Particularly, it is assumed but not yet demonstrated that physiotherapy may support preservation of function and reduce the risk of adverse events related to GC use. Patients may benefit from exercise by maintaining muscle mass and function as well as by fall prevention especially in the frail. What is the role of diet in PMR and nutrition supplements (eg, fish oil) related to outcomes?
10. What is the efficacy and safety of herbal preparations in PMR?
11. What is the role of imaging (particularly ultrasound) for the assessment and monitoring of PMR, identification of overlap with other diseases (eg, large vessel vasculitis or inflammatory arthritis) alongside clinical and patient reported outcomes?
12. **Which biomarkers may be useful in PMR? Why do some patients do better than others? How can we identify these groups and what is the biological mechanism behind it? Should different drugs be applied to different PMR subgroups?**
13. What is the morbidity and mortality of PMR patients (with a particular focus on cardiovascular risk) in long-term observational studies?
14. What is the etiopathogenesis of PMR? Which targeted therapies could be developed based on new knowledge of disease mechanisms?

Bolded points indicate the top 5 items of the research agenda according to the opinion of the guideline panel.

to GC or patients experiencing GC-related adverse events. The group further agreed that MTX may be used with oral or i.m. GC preparations even if the concomitant use of MTX and i.m. methylprednisolone has not been tested formally.

The efficacy of MTX was addressed in four randomized controlled trials and one retrospective study testing the use of MTX plus oral GCs (initial prednisone doses ranging from 15 to 25 mg/day) (24–27,51). There was moderate to high quality of evidence (QoE) from studies indicating a benefit of MTX regarding remission (1 study) (27), relapse rate (1 study) (24), discontinuation of GC (1 study) (24) and cumulative GC doses (3 studies) (24,26,27). Evidence from one to four studies (1 related to remission, 4 to relapse, 1 to discontinuation of GC) indicating no benefit regarding these outcomes was of very low quality (25–27,51).

The reasons why the panel did not support a stronger recommendation for the use of MTX in PMR are the following: 1) the total number of patients investigated in randomized trials was small (n=194) (24–27), hence further confirmation of the present data is necessary; 2) results were contradictory in part, although trials with a negative result had a very low QoE; 3) a reduction in GC-related adverse events with the use of MTX has not been demonstrated. The power of the prospective studies to address this outcome, however, was insufficient. The panel nevertheless felt that earlier discontinuation of GC (24) and a lower cumulative GC dose in MTX users (26,27) decreases the likelihood of GC-related side effects; and 4) the cost-effectiveness of MTX use in PMR is not clear. More frequent prescriptions of MTX may lead to higher utilization of healthcare resources in the short term (eg, because of specialist referral, monitoring visits, blood tests, etc.) but may in the long term save costs by reducing GC-related side effects. Future studies are necessary to clarify this issue.

The group recognized that no recommendation can be made for the use of other non-biologic (ie, conventional synthetic and conventional targeted) DMARDs in PMR because of the lack of good evidence from PMR studies. Hydroxychloroquine was investigated by a single very low QoE retrospective study reporting no benefit regarding relapse rate (51).

Recommendation 8: (PICOs 10–11) The panel strongly recommends against the use of TNFα blocking agents for the treatment of PMR.

The group agreed strongly against the use of TNFα blocking agents in PMR at this time since there is no evidence for benefit, but there is a considerable risk of potential harm and high resource use (55).

No recommendation can be made for other biologic agents as no prospective trials have been published so far. There is one ongoing randomized study on the

use of tocilizumab (clinicaltrials.gov NCT01396317) and another three-arm trial comparing secukinumab, canakinumab and GCs (clinicaltrials.gov NCT01364389) in PMR. The results of these studies may lead to a modification of this recommendation.

Recommendation 9: (PICO 12) The panel conditionally recommends considering an individualized exercise program for PMR patients aimed at the maintenance of muscle mass and function, and reducing risk of falls.

There are no studies investigating the value of non-pharmacological therapies (eg, physiotherapy, relaxation techniques, diets, etc.) in PMR and there is insufficient clinical experience on this issue to agree on a specific recommendation. Nevertheless, the panel agreed on recommending an individualized exercise program (see overarching principles) in view of its benefit for maintaining muscle mass and function and reducing risk of falls, especially in older persons on long-term GCs as well as in frail patients.

Use of herbal preparations in PMR. The panel strongly recommends against the use of the Chinese herbal preparations Yanghe and Biqi capsules in PMR patients.

There were some discussions about whether herbal preparations could be considered non-pharmacological interventions (and were therefore within the scope of PICO 12); however, the panel felt the need for comment on this issue because several preparations are available which may be popular with PMR patients.

The SLR identified two studies testing Chinese Yanghe herb decoction and Chinese Biqi capsules in PMR patients (56,57). For Chinese Yanghe there is moderate QoE for a lower ESR at week 8 (mean difference 6.0 mm/hour) and 12 (6.4 mm/hour) and very low QoE indicating a lower rate of GC-related adverse events (with borderline significance of the effect estimate) as well as reduced morning stiffness at week 12 (56). For Biqi capsules there is low QoE indicating a higher response rate at week 12 (57).

The group nevertheless agreed (after balancing evidence, benefit/harm, availability and resource use) to recommend strongly against the regular use of these preparations at this time for the following reasons: 1) the relevance of the small effect of Chinese Yanghe herb decoction on ESR is minimal for patients and good evidence for a clinical benefit of the substance is not available; 2) neither of the two substances is approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA); 3) the generalizability of the evidence for benefit is unclear; 4) these preparations may have unforeseeable adverse effects; 5) the availability of high quality preparations is unclear; and 6) resource impact (ie, costs) is unknown.

Release and implementation of the recommendations. See online supplementary file S2, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39333/abstract.

Cost implications and conflicts of interest. Cost implications are outside the scope of these recommendations.

None of the panel members disclosed any conflict of interest associated with the development of these recommendations.

Discussion

See online supplementary file S3 (http://onlinelibrary.wiley.com/doi/10.1002/art.39333/abstract) for a full-length discussion. The 2015 EULAR/ACR recommendations for the management of PMR is the first collaborative project between EULAR and ACR to endorse treatment recommendations in rheumatology.

We recognize that our recommendations are only partially supported by evidence, and that they do not cover all aspects important for the management of PMR. The group therefore unanimously agreed that the research agenda (containing the evidence gaps related to PMR management) is an important result of this project (Box 2).

Due to our rigorous SLR approach to select high quality papers, we did not include other reviews, case reports or case series indicating possible treatment options in treatment-resistant PMR patients. For example, we found one earlier SLR reporting similar conclusions regarding the value of MTX in PMR (58). In addition, two case series were recently published on the use of leflunomide (59,60) and a few case reports are available on tocilizumab (61–63). Azathioprine has been tested in a double-blind randomized controlled trial in patients with PMR and GCA; however, as PMR patients were not analyzed separately, we did not include this study in the SLR (64).

It was beyond the scope of this recommendation project to define treatment targets in PMR. "Clinical improvement" was considered as the first treatment goal after the initiation of GCs, and the response criteria used in the 2012 classification criteria study may be considered (3,4). Remission and relapse have been heterogeneously defined in the literature, as we pointed out previously (65). Future prospective studies aimed at the validation of new definitions of response, remission and relapse are, therefore, required to enable a targeted treatment approach in PMR (66).

The most important limitations of this project are the paucity of high quality trials (as mentioned above) and the fact that GRADE is less well developed for the assessment of rare outcomes. Consequently, the QoE for

adverse events is usually lower than for efficacy data. This necessitated the use of relevant external evidence to strengthen this aspect of our recommendations.

These recommendations should support clinicians to achieve the best patient outcomes. Further research on existing drugs is necessary to offer additional, evidence-based treatment options to our patients. We anticipate an update of these recommendations 3 years after their publication; however, an earlier revision may be necessary if new data emerge that would modify the current recommendations.

ACKNOWLEDGMENT

We thank Catherine Wardle from Southend library for her assistance retrieving full text articles.

AUTHOR CONTRIBUTIONS

All authors contributed to conception and design of the study, acquisition and/or interpretation of data, drafting the article or revising it critically for important intellectual content, and approved the final version of the manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Arthritis Care & Research
Vol. 73, No. 8, August 2021, pp 1088–1105
DOI 10.1002/acr.24634
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2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

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Objective. To provide evidence-based recommendations and expert guidance for the management of antineutrophil cytoplasmic antibody–associated vasculitis (AAV), including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Methods. Clinical questions regarding the treatment and management of AAV were developed in the population, intervention, comparator, and outcome (PICO) format (47 for GPA/MPA, 34 for EGPA). Systematic literature reviews were conducted for each PICO question. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to assess the quality of evidence and formulate recommendations. Each recommendation required ≥70% consensus among the Voting Panel.

Results. We present 26 recommendations and 5 ungraded position statements for GPA/MPA, and 15 recommendations and 5 ungraded position statements for EGPA. This guideline provides recommendations for remission induction and maintenance therapy as well as adjunctive treatment strategies in GPA, MPA, and EGPA. These recommendations include the use of rituximab for remission induction and maintenance in severe GPA and MPA and the use of mepolizumab in nonsevere EGPA. All recommendations are conditional due in part to the lack of multiple randomized controlled trials and/or low-quality evidence supporting the recommendations.

Conclusion. This guideline presents the first recommendations endorsed by the American College of Rheumatology and the Vasculitis Foundation for the management of AAV and provides guidance to health care professionals on how to treat these diseases.

INTRODUCTION

The antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV) comprise granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). These diseases affect small- and medium-sized vessels and are characterized by multisystem organ involvement.

GPA is characterized histologically by necrotizing granulomatous inflammation in addition to vasculitis. Common clinical manifestations include destructive sinonasal lesions, pulmonary nodules, and pauci-immune glomerulonephritis. GPA is most commonly associated with cytoplasmic ANCA and antibodies to proteinase 3 (PR3). Among European populations, prevalence ranges from 24 to 157 cases per million, with the highest prevalence reported in Sweden and the UK (1).

MPA is characterized histologically by vasculitis without granulomatous inflammation. Common clinical manifestations include rapidly progressive pauci-immune glomerulonephritis and alveolar hemorrhage. MPA is most commonly associated with perinuclear ANCA and antibodies to myeloperoxidase. The prevalence of MPA ranges from 0 to 66 cases per million among European countries and 86 cases per million in Japan (1,2).

EGPA is characterized histologically by eosinophilic tissue infiltration in addition to vasculitis. Common clinical manifestations include asthma, peripheral eosinophilia, and peripheral neuropathy. Only 40% of patients produce detectable ANCA. The overall prevalence of EGPA in European populations has been estimated to range from 2 to 38 cases per million (1,3).

Prior to the use of alkylating agents, survival with these diseases was quite poor (e.g., median survival of patients with GPA was ~5 months) (4). Current treatment regimens have reversed this poor prognosis, but treatments are still associated with toxicity. Recent clinical trials have investigated the efficacy and toxicity of both biologic and nonbiologic immunosuppressive agents for the treatment of AAV. Observational studies have provided additional insight regarding management strategies for these diseases. Therefore, this guideline was developed to provide evidence-based recommendations for the treatment and management of GPA, MPA, and EGPA. Although this guideline may inform an international audience, these recommendations were developed considering the experience with and availability of treatment and diagnostic options in the US.

METHODS

This guideline followed the American College of Rheumatology (ACR) guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and develop recommendations (5,6). ACR policy guided the management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis). Supplementary Appendix 1 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract) presents a detailed description of the methods. Briefly, the Literature Review team undertook systematic literature reviews for predetermined questions addressing specific clinical populations, interventions,

The article is published simultaneously in *Arthritis & Rheumatology*.

Supported by the American College of Rheumatology and the Vasculitis Foundation.

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Dr. Langford has received consulting fees, speaking fees, and/or honoraria from Bristol Myers Squibb (less than $10,000) and research grants from Bristol Myers Squibb, GlaxoSmithKline, and Genentech. Dr. Grayson has submitted a patent application for the diagnosis and treatment of vacuoles, E1 enzyme, x-linked, autoinflammatory, somatic (VEXAS) syndrome. Dr. Merkel has received consulting fees, speaking fees, and/or honoraria from AbbVie, Biogen, Bristol Myers Squibb, CSL Behring, Genentech/Roche, Sanofi-Genzyme, GlaxoSmithKline, Insmed, Janssen, Kiniksa, Kyverna, Pfizer, Sparrow, and Takeda (less than $10,000 each) and from AstraZeneca, InflaRx, and ChemoCentryx (more than $10,000 each), research support from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, ChemoCentryx, Forbius, Genetech/Roche, Sanofi-Genzyme, GlaxoSmithKline, and InflaRx, and royalties from *UpToDate*. Dr. Stone has received consulting fees, speaking fees, and/or honoraria from Roche and Genentech (less than $10,000 each). Dr. Sule holds a patent related to the development of the Glucocorticoid Toxicity Index. Dr. Sundel has received royalties from *UpToDate*. Dr. Dua has received consulting fees, speaking fees, and/or honoraria from ChemoCentryx and AbbVie (less than $10,000 each). No other disclosures relevant to this article were reported.

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Submitted for publication September 25, 2020; accepted in revised form April 13, 2021.

comparators, and outcomes (PICO). An in-person Patient Panel of 11 individuals with different types of vasculitis (4 patients with GPA, 1 patient with MPA, and 2 patients with EGPA) was moderated by a member of the Literature Review team (ABD). This Patient Panel reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives and preferences. The Voting Panel comprised 9 adult rheumatologists, 5 pediatric rheumatologists, and 2 patients; they reviewed the Literature Review team's evidence summaries and, bearing in mind the Patient Panel's deliberations, formulated and voted on recommendations.

The Voting Panel was assembled for the ACR and Vasculitis Foundation's broad effort to develop recommendations for 7 forms of systemic vasculitis: giant cell arteritis, Takayasu arteritis, polyarteritis nodosa, Kawasaki syndrome, and the 3 AAVs presented in this report. The physicians on this panel included rheumatologists who could provide insight on all of these diseases and did not include other subspecialists who would not have experience with many of the other vasculitides addressed in this effort (e.g., pulmonologists who would not have experience with large- or medium-sized vessel vasculitis). The Literature Review team chair was a nephrologist. The patients on the Voting Panel presented the views of the Patient Panel, which consisted of patients with different types of vasculitis. A recommendation required ≥70% consensus among the Voting Panel.

How to interpret the recommendations

A *strong* recommendation is usually supported by moderate- to high-quality evidence (e.g., multiple randomized controlled trials). For a strong recommendation, the recommended course of action would apply to all or almost all patients. Only a small proportion of clinicians/patients would not want to follow the recommendation. In rare instances, a strong recommendation may be based on very low– to low-certainty evidence. For example, an intervention may be strongly recommended if it is considered benign, low-cost, without harms, and the consequence of not performing the intervention may be catastrophic. An intervention may be strongly recommended against if there is high certainty that the intervention leads to more harm than the comparison with very low or low certainty about its benefit (7).

Table 1. Definitions of selected terms used in the recommendations and ungraded position statements for GPA, MPA, and EGPA*

Term	Definition
Disease states	
Active disease	New, persistent, or worsening clinical signs and/or symptoms attributed to GPA, MPA, or EGPA and not related to prior damage
Severe disease	Vasculitis with life- or organ-threatening manifestations (e.g., alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, limb/digit ischemia)
Nonsevere disease	Vasculitis without life- or organ-threatening manifestations (e.g., rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis)
Remission	Absence of clinical signs or symptoms attributed to GPA, MPA, or EGPA, on or off immunosuppressive therapy
Refractory disease	Persistent active disease despite an appropriate course of immunosuppressive therapy
Relapse	Recurrence of active disease following a period of remission
Treatments	
IV pulse GCs	IV methylprednisolone 500–1,000 mg/day (adults) or 30 mg/kg/day (children; maximum 1,000 mg/day) or equivalent for 3–5 days
High-dose oral GCs	Prednisone 1 mg/kg/day (adults; generally up to 80 mg/day) or 1–2 mg/kg/day (children; generally up to 60 mg/day) or equivalent
Remission induction therapy	
Methotrexate	Up to 25 mg/week (SC or oral)
Azathioprine	Up to 2 mg/kg/day
Mycophenolate mofetil	Up to 1,500 mg (oral) twice per day
Cyclophosphamide	Up to 2 mg/kg/day (oral) for 3–6 months; or intermittent 15 mg/kg (IV) every 2 weeks for 3 doses, followed by 15 mg/kg (IV) every 3 weeks for at least 3 doses (adults)
Rituximab	375 mg/m^2 (IV) weekly for 4 doses or 1,000 mg on days 1 and 15 (adults); or 375 mg/m^2 (IV) weekly for 4 doses or 575 mg/m^2 for patients with body surface area ≤1.5m^2 or 750 mg/m^2 for patients with body surface area >1.5m^2 with a typical maximum of 1 gm per infusion (both for 2 doses, days 1 and 15) (children)
Mepolizumab	300 mg (SC) every 4 weeks (adults)
Remission maintenance therapy	
Methotrexate, azathioprine, mycophenolate mofetil	Same dosing regimen as in remission induction therapy
Rituximab	500 mg (IV) every 6 months or 1 gm (IV) every 4 months (adults), 250 mg/m^2 (IV) every 6 months (children), or other doses
Mepolizumab	300 mg (SC) every 4 weeks
Omalizumab	300–600 mg (SC) every 2–4 weeks

* GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; EGPA = eosinophilic granulomatosis with polyangiitis; IV = intravenous; GCs = glucocorticoids; SC = subcutaneous.

A *conditional* recommendation is usually supported by lower-quality evidence or a close balance between desirable and undesirable outcomes. For a conditional recommendation, the recommended course of action would apply to the majority of the patients, but the alternative is a reasonable consideration. Conditional recommendations always warrant a shared decision-making approach. We specify some conditions under which the alternative may be considered.

In some instances, the committee found that the evidence for a particular PICO question did not support a graded recommendation or did not favor one intervention over the other. However, the Voting Panel believed that the PICO question addressed a commonly encountered clinical question and thus felt that providing guidance for this question was warranted. For these situations, we present "ungraded position statements," which reflect general views of the Voting Panel.

In this evidence-based guideline, we explicitly used the best evidence available and present it for the clinician and reader (8). In some instances, this includes randomized trials in which the interventions under consideration are directly compared. The GRADE system rates evidence that comes exclusively from the collective experience of the Voting Panel and Patient Panel members as "very low quality" evidence (6).

For each recommendation, details regarding the PICO questions and the GRADE evidence tables can be found in Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract).

RESULTS

For the evidence report for GPA and MPA, the Literature Review team reviewed 729 articles to address 47 PICO questions. For the evidence report for EGPA, 190 articles were reviewed to address 34 PICO questions.

Recommendations and ungraded position statements for GPA and MPA

GPA and MPA are recognized as different diseases for which disease-specific management approaches exist. However, many recommendations and ungraded position statements consider GPA and MPA together, because pivotal trials have enrolled both groups and presented results for these diseases together. Therefore, we present recommendations and ungraded position statements applicable to both GPA and MPA as well as recommendations and ungraded position statements only applicable to GPA. All recommendations for GPA/MPA are conditional, due in part to a lack of multiple randomized controlled trials supporting the recommendations. The complete list of studies reviewed to form the recommendations is provided in the evidence report (Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract). Given that these diseases affect multiple organ systems, collaboration between rheumatologists, nephrologists, pulmonologists, and otolaryngologists can enhance the care of patients with GPA and MPA.

Table 1 presents the definitions of selected terms used in the recommendations and ungraded position statements, including the definition of severe and nonsevere disease and the dosing regimens of medications used for remission induction and maintenance. Table 2 presents the recommendations and ungraded position statements with their supporting PICO questions and levels of evidence. Figure 1 presents key recommendations for the treatment of GPA and MPA.

Remission induction for active, severe disease

Recommendation: For patients with active, severe GPA/MPA, we conditionally recommend treatment with rituximab over cyclophosphamide for remission induction.

Both rituximab and cyclophosphamide, in combination with glucocorticoids, have been used for remission induction in GPA and MPA. Rituximab has been shown to provide similar benefits to cyclophosphamide for remission induction in a randomized controlled trial (9). Although the currently used cumulative doses of cyclophosphamide are lower than previous regimens and result in less toxicity per treatment course, rituximab is still preferred, since rituximab is considered less toxic than cyclophosphamide. A single course of cyclophosphamide can carry substantial risks such as neutropenia, bladder injury, and the small but present potential for infertility which can be devastating to a young patient. Risks of malignancy and infertility increase when repeated courses of cyclophosphamide are used. Rituximab was also preferred by the Patient Panel, as a generally better-tolerated treatment. Retrospective studies suggest that the 2 remission induction regimens for rituximab used in adults (375 mg/m^2 every week for 4 weeks [US Food and Drug Administration (FDA)–approved dosing schedule] and 1,000 mg on days 1 and 15) are equally efficacious. The choice between these regimens should be guided by the patient's preferences and values.

Cyclophosphamide (dosing provided in Table 1) may be used when rituximab needs to be avoided or when patients have active disease despite receiving rituximab treatment. It remains controversial whether cyclophosphamide should be preferred for certain types of severe disease, such as acute renal failure (e.g., serum creatinine >4.0 mg/dl). Either intravenous (IV) pulse or daily oral cyclophosphamide can be used (10,11). For adults, the decision between these 2 options should be based on patient and physician preferences. In children, IV cyclophosphamide may be preferred to facilitate compliance and limit toxicity. Data regarding the efficacy of combined cyclophosphamide and rituximab therapy for remission induction remain limited (12), and potential toxicity of this combination remains a concern. The combination of rituximab with cyclophosphamide is not widely used in the US, and its efficacy compared to rituximab

Table 2. Recommendations/statements for the management of GPA and MPA*

Recommendation/statement	PICO question informing recommendation and discussion	Level of evidence
Remission induction for active, severe disease		
Recommendation: For patients with active, severe GPA/MPA, we conditionally recommend treatment with rituximab over cyclophosphamide for remission induction.	4, 5, 6	Very low to moderate
Recommendation: In patients with GPA/MPA with active glomerulonephritis, we conditionally recommend *against* the routine addition of plasma exchange to remission induction therapy.	34	Low to high
Recommendation: In patients with active, severe GPA/MPA with alveolar hemorrhage, we conditionally recommend *against* adding plasma exchange to remission induction therapies.	35	Low to high
Ungraded position statement: For patients with active, severe GPA/MPA, either IV pulse GCs or high-dose oral GCs may be prescribed as part of initial therapy.	2	Very low to moderate
Recommendation: In patients with active, severe GPA/MPA, we conditionally recommend a reduced-dose GC regimen over a standard-dose GC regimen for remission induction.	3	Very low to moderate
Remission induction for active, nonsevere disease		
Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate over cyclophosphamide or rituximab.	12, 13	Very low to moderate
Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and GCs over GCs alone.	14	Low
Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and GCs over azathioprine and GCs or mycophenolate mofetil and GCs.	8, 9, 10	Low
Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and GCs over trimethoprim/sulfamethoxazole and GCs.	11	Low
Remission maintenance		
Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with rituximab over methotrexate or azathioprine for remission maintenance.	15, 16, 17, 18	Very low to moderate
Recommendation: For patients with GPA/MPA who are receiving rituximab for remission maintenance, we conditionally recommend scheduled re-dosing over using ANCA titers or CD19+ B cell counts to guide re-dosing.	24, 25	Very low to low
Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with methotrexate or azathioprine over mycophenolate mofetil for remission maintenance.	19	Very low to moderate
Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with methotrexate or azathioprine over leflunomide for remission maintenance.	20	Very low to low
Recommendation: For patients with GPA whose disease has entered remission, we conditionally recommend treatment with methotrexate or azathioprine over trimethoprim/sulfamethoxazole for remission maintenance.	21, 22	Very low to low
Recommendation: In patients with GPA whose disease has entered remission, we conditionally recommend *against* adding trimethoprim/sulfamethoxazole to other therapies (e.g., rituximab, azathioprine, methotrexate, etc.) for the purpose of remission maintenance.	23	Low to moderate
Recommendation: For patients with GPA/MPA receiving remission maintenance therapy with rituximab who have hypogammaglobulinemia (e.g., IgG <3 gm/liter) and recurrent severe infections, we conditionally recommend immunoglobulin supplementation.	44	Very low
Ungraded position statement: The duration of non-GC remission maintenance therapy in GPA/MPA should be guided by the patient's clinical condition, preferences, and values.	26	Low to moderate
Ungraded position statement: The duration of GC therapy for GPA/MPA should be guided by the patient's clinical condition, preferences, and values.	27, 33	Low to moderate
Treatment of disease relapse		
Recommendation: For patients with GPA/MPA who have experienced relapse with severe disease manifestations and are not receiving rituximab for remission maintenance, we conditionally recommend treatment with rituximab over cyclophosphamide for remission re-induction.	28	Low
Recommendation: For patients with GPA/MPA who experienced relapse with severe disease manifestations while receiving rituximab for remission maintenance, we conditionally recommend switching from rituximab to cyclophosphamide over receiving additional rituximab for remission re-induction.	29	Very low
Treatment of refractory disease		
Recommendation: For patients with severe GPA/MPA that is refractory to treatment with rituximab or cyclophosphamide for remission induction, we conditionally recommend switching treatment to the other therapy over combining the 2 therapies.	30	Very low
Recommendation: For patients with GPA/MPA that is refractory to remission induction therapy, we conditionally recommend adding IVIG to current therapy.	31	Low to moderate

(Continued)

Table 2. *(Cont'd)*

Recommendation/statement	PICO question informing recommendation and discussion	Level of evidence
Treatment of sinonasal, airway, and mass lesions		
Ungraded position statement: For patients with sinonasal involvement in GPA, nasal rinses and topical nasal therapies (antibiotics, lubricants, and GCs) may be beneficial.	36, 37, 38, 39	Very low to low
Recommendation: For patients with GPA in remission who have nasal septal defects and/or nasal bridge collapse, we conditionally recommend reconstructive surgery, if desired by the patient.	45	Low
Recommendation: For patients with GPA and actively inflamed subglottic and/or endobronchial tissue with stenosis, we conditionally recommend treating with immunosuppressive therapy over surgical dilation with intralesional GC injection alone.	40	Low
Recommendation: For patients with GPA and mass lesions (e.g., orbital pseudotumor or masses of the parotid glands, brain, or lungs), we conditionally recommend treatment with immunosuppressive therapy over surgical removal of the mass lesion with immunosuppressive therapy.	41, 42	Very low to low
Other considerations		
Recommendation: In patients with GPA/MPA, we conditionally recommend *against* dosing immunosuppressive therapy based on ANCA titer results alone.	1	Very low
Recommendation: For patients with GPA who are receiving rituximab or cyclophosphamide, we conditionally recommend prophylaxis to prevent *Pneumocystis jirovecii* pneumonia.	43	Low
Recommendation: For patients with GPA/MPA in remission and stage 5 chronic kidney disease, we conditionally recommend evaluation for renal transplantation.	46	Low
Recommendation: For patients with active GPA/MPA who are unable to receive other immunomodulatory therapy, we conditionally recommend administering IVIG.	32	Low
Ungraded position statement: The optimal duration of anticoagulation is unknown for patients with GPA/MPA who experience venous thrombotic events.	47	Very low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract). IV = intravenous; GCs = glucocorticoids; ANCA = antineutrophil cytoplasmic antibody; IVIG = IV immunoglobulin.

or cyclophosphamide monotherapy is not established. This combination remains under study (ClinicalTrials.gov identifier: NCT03942887) at this time.

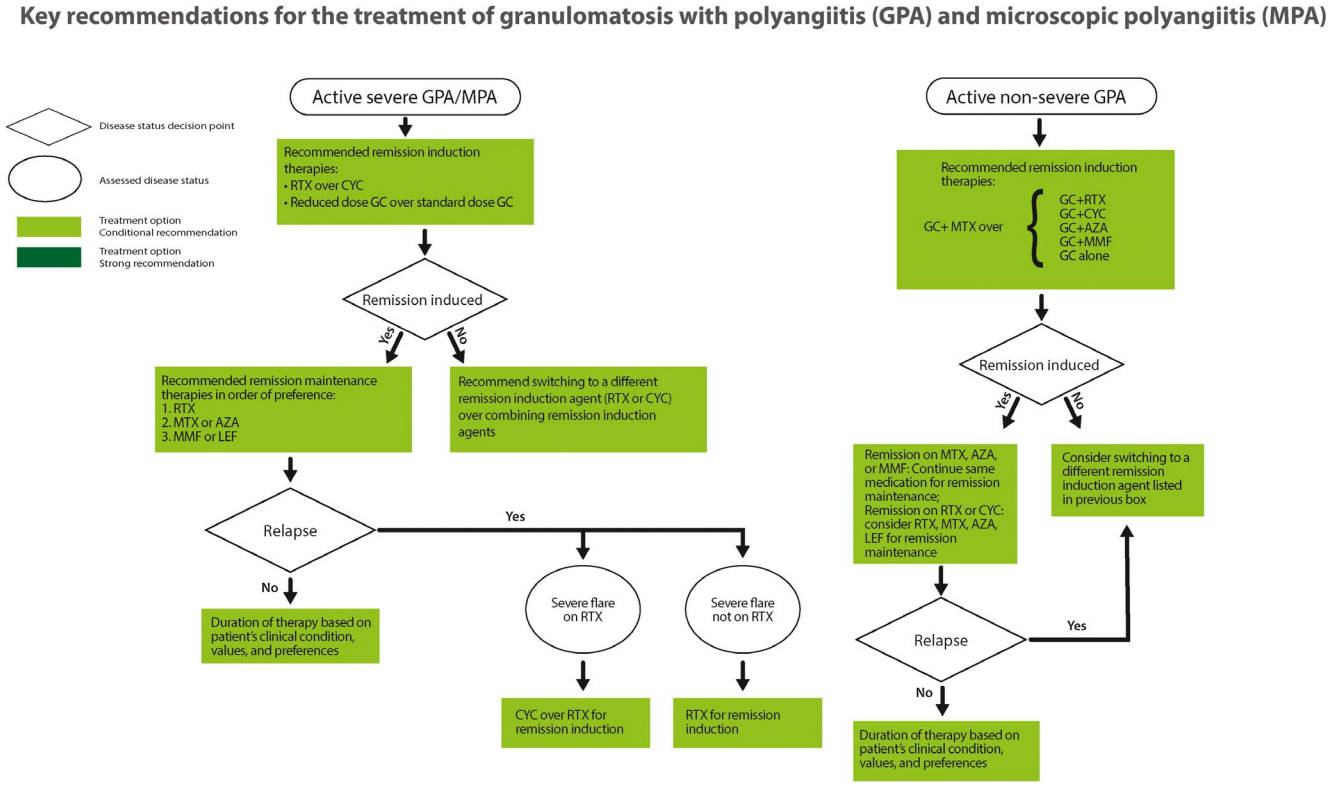
Recommendation: In patients with GPA/MPA with active glomerulonephritis, we conditionally recommend *against* the routine addition of plasma exchange to remission induction therapy.

Plasma exchange should not be initiated in all patients with active glomerulonephritis but can be considered for patients at higher risk of progression to end-stage renal disease (ESRD) who accept a potential increased risk of infection.

This recommendation is supported by data from the 2 largest trials of plasma exchange for the treatment of glomerulonephritis in AAV. The first trial, which required a serum creatinine level of ≥5.8 mg/dl for entry, showed that plasma exchange decreased the risk of ESRD but did not decrease mortality (13,14). In a more recent randomized trial of plasma exchange in AAV, the addition of plasma exchange to conventional remission induction therapy did not improve the composite outcome of ESRD or death; a decrease in the risk of ESRD was observed, but the result was not statistically significant (hazard ratio 0.81 [95% confidence interval (95% CI) 0.57–1.13]) (15).

However, combined data from these 2 trials show that there is probably a decreased risk of ESRD in patients with glomerulonephritis who received plasma exchange, compared to those who did not (hazard ratio 0.72 [95% CI 0.53–0.98]; moderate certainty) (Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract). The benefit was most pronounced in patients with the highest risk of ESRD (118 fewer cases of ESRD per 1,000 cases of active glomerulonephritis [95% CI between 217 and 7 fewer cases]), although no difference in mortality was demonstrated (risk ratio 1.15 [95% CI 0.78–1.70]; moderate certainty). In 4 trials of plasma exchange in AAV, a higher risk of severe infection was observed with plasma exchange (risk ratio 1.19 [95% CI 0.99–1.42]; moderate certainty).

These findings suggest that for patients with a low risk of progression to ESRD, the risk of plasma exchange may outweigh the benefit; however, in patients with a higher risk of progression to ESRD, the decrease in risk could outweigh the increased risk of serious infection with plasma exchange. Therefore, the Voting Panel does not recommend plasma exchange for all patients with active glomerulonephritis but favors consideration of the treatment for patients at a higher risk of progression to ESRD. Factors that could influence whether plasma exchange is initiated include the patient's kidney function upon presentation, rate of loss of kidney function, response to remission induction therapies, and the patient's ability to tolerate serious infections.


Key recommendations for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)
Disease status decision point
Assessed disease status
Treatment option
Conditional recommendation
Treatment option
Strong recommendation
Active severe GPA/MPA
Recommended remission induction therapies:
• RTX over CYC
• Reduced dose GC over standard dose GC
Remission induced
Yes
No
Recommended remission maintenance therapies in order of preference:
1. RTX
2. MTX or AZA
3. MMF or LEF
Recommend switching to a different remission induction agent (RTX or CYC) over combining remission induction agents
Relapse
Yes
No
Duration of therapy based on patient's clinical condition, values, and preferences
Severe flare on RTX
Severe flare not on RTX
CYC over RTX for remission induction
RTX for remission induction
Active non-severe GPA
Recommended remission induction therapies:
GC+ MTX over
GC+RTX
GC+CYC
GC+AZA
GC+MMF
GC alone
Remission induced
Yes
No
Remission on MTX, AZA, or MMF: Continue same medication for remission maintenance;
Remission on RTX or CYC: consider RTX, MTX, AZA, LEF for remission maintenance
Consider switching to a different remission induction agent listed in previous box
Relapse
Yes
No
Duration of therapy based on patient's clinical condition, values, and preferences

AZA = azathioprine, CYC = cyclophosphamide, GC = glucocorticoids, LEF = leflunomide, MMF = mycophenolate mofetil, MTX = methotrexate, RTX = rituximab

Figure 1. Key recommendations for the treatment of granulomatosis with polyangiitis and microscopic polyangiitis.

Plasma exchange remains advisable in patients with GPA or MPA who also have anti–glomerular basement membrane disease.

Recommendation: In patients with active, severe GPA/MPA with alveolar hemorrhage, we conditionally recommend *against* adding plasma exchange to remission induction therapies.

Two trials evaluated the use of plasma exchange in patients presenting with alveolar hemorrhage, and no differences in mortality or remission rates were observed. Thus, plasma exchange does not have an established benefit for patients with alveolar hemorrhage and is associated with an increased risk of serious infection (see above recommendation). Plasma exchange may be considered for certain patients with active glomerulonephritis or those who are critically ill and whose disease is not responding to recommended remission induction therapies (i.e., plasma exchange as "salvage" or "rescue" therapy).

Plasma exchange remains advisable in patients with GPA or MPA who also have anti–glomerular basement membrane disease.

Ungraded position statement: For patients with active, severe GPA/MPA, either IV pulse glucocorticoids or high-dose oral glucocorticoids may be prescribed as part of initial therapy.

There are no trials comparing the efficacy of IV pulse glucocorticoids to high-dose oral glucocorticoids. Higher doses of glucocorticoids (such as pulse glucocorticoids) are generally administered to patients with organ- or life-threatening disease manifestations but may be associated with an increased risk of infection (16).

Recommendation: For patients with active, severe GPA/MPA, we conditionally recommend a reduced-dose glucocorticoid regimen over a standard-dose glucocorticoid regimen for remission induction.

A recent study demonstrated that a reduced-dose glucocorticoid regimen provided a similar benefit compared to a standard-dose regimen for the composite outcome of ESRD or death, and was associated with a decreased risk of infection (15). Due to the known toxicities associated with long-term glucocorticoid use, minimizing glucocorticoid exposure is critical to improving outcomes. Glucocorticoid dosing may be individualized for each patient. Of note, the reduced-dose regimen started with pulse methylprednisolone (3 daily pulses for maximum total dose of 3 gm) and 1 week of high-dose oral glucocorticoids. The dosing regimens used in this study are described in Supplementary Appendix 3 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract).

Remission induction for active, nonsevere disease

Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate over cyclophosphamide or rituximab.

Nonsevere GPA is defined as GPA without life- or organ-threatening manifestations (Table 1). Methotrexate, rituximab, and cyclophosphamide are effective at inducing remission in this patient

group (11). However, like severe GPA, nonsevere GPA can be a chronic disease that requires multiple courses of therapy. Thus, the Voting Panel favored using therapies with potentially less toxicity before utilizing therapies with potentially more toxicity. Therefore, methotrexate is preferred due to the greater toxicity of cyclophosphamide. Methotrexate is currently recommended over rituximab because of the larger body of evidence and clinical experience with methotrexate treatment for this patient group; clinical trials are needed to compare their efficacy. Rituximab may be preferred in specific clinical situations, including for patients with hepatic or renal dysfunction, recurrent relapses while receiving methotrexate, or concerns regarding compliance.

Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and glucocorticoids over glucocorticoids alone.

Methotrexate with glucocorticoids is recommended to minimize glucocorticoid exposure and toxicity. Overall, there are few clinical situations in which treatment with glucocorticoid monotherapy may be considered (e.g., arthralgias or inability to tolerate other remission maintenance therapies), and close monitoring is needed if this treatment strategy is used.

Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and glucocorticoids over azathioprine and glucocorticoids or mycophenolate mofetil and glucocorticoids.

The use of methotrexate for remission induction in this patient group is supported by more available data than other treatments (11), but azathioprine and mycophenolate mofetil can be considered. Comparative effectiveness trials are needed to evaluate the efficacy of methotrexate, azathioprine, and mycophenolate mofetil for remission induction in active, nonsevere GPA. Clinical factors may influence the medication selected. For example, methotrexate should be used with caution or avoided in patients with moderate-to-severe renal insufficiency. Azathioprine is the preferred agent for pregnant patients or in patients who cannot tolerate methotrexate or mycophenolate mofetil, while methotrexate or mycophenolate mofetil is indicated in patients with total thiopurine S-methyltransferase deficiency or high-risk *TPMT* and/or *NUDT15* genotypes.

Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and glucocorticoids over trimethoprim/sulfamethoxazole and glucocorticoids.

Methotrexate is considered more effective than trimethoprim/sulfamethoxazole for remission induction, based on previous findings (17). Low-dose trimethoprim/sulfamethoxazole may be administered concurrently with immunosuppressive agents to prevent *Pneumocystis jirovecii* pneumonia (see GPA/MPA recommendation on this topic).

Remission maintenance

Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with rituximab over methotrexate or azathioprine for remission maintenance.

Rituximab is associated with a lower relapse rate than azathioprine when used for remission maintenance after remission induction with cyclophosphamide (18). Methotrexate and azathioprine have comparable efficacy rates for remission maintenance (19). Therefore, rituximab is favored over methotrexate or azathioprine. However, more long-term safety data are available for methotrexate and azathioprine, and cost and other factors may limit rituximab use.

Different doses of rituximab have been used for remission maintenance, including IV 500 mg every 6 months (18) (FDA-approved), IV 1,000 mg every 4 months (20), and IV 1,000 mg every 6 months (21). No comparative trials have been conducted. Thus, the optimal dose of rituximab for remission maintenance remains uncertain.

If methotrexate or azathioprine treatment is being considered for remission maintenance, the patient's clinical situation, preferences, and values should guide selection between them, given their comparable efficacy.

Recommendation: For patients with GPA/MPA who are receiving rituximab for remission maintenance, we conditionally recommend scheduled re-dosing over using ANCA titers or CD19+ B cell counts to guide re-dosing.

In one randomized trial, patients who received rituximab for remission maintenance based on changes in CD19+ B cell counts and/or ANCA titers had similar rates of relapse as those receiving rituximab as a scheduled dose. However, this study was limited by the small sample size, and there were wide CIs for the effect size (22). This recommendation is based in part on the experience and expertise of the Voting Panel, which recognized that flares can occur when patients experience CD19+ B cell depletion and/or when test results for ANCA are negative. Thus, CD19+ B cell counts or ANCA titers may not accurately indicate the potential for a patient's disease to flare.

Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with methotrexate or azathioprine over mycophenolate mofetil for remission maintenance.

Methotrexate and azathioprine are equally efficacious for remission maintenance (19). Azathioprine is favored over mycophenolate mofetil because the relapse rate with mycophenolate mofetil was higher than with azathioprine when studied with remission maintenance (23). Mycophenolate mofetil may still be considered for those unable to tolerate or with contraindications to methotrexate, azathioprine, or rituximab.

Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with methotrexate or azathioprine over leflunomide for remission maintenance.

Methotrexate or azathioprine treatment is recommended over leflunomide due to the data supporting and clinical experience using methotrexate and azathioprine for remission maintenance. The data and clinical experience with leflunomide are more limited. In one clinical trial comparing leflunomide to methotrexate treatment, leflunomide treatment demonstrated a decreased rate of relapse but a higher rate of drug withdrawal (24). The trial used a leflunomide dose of 30 mg/day, which may have contributed to toxicity.

Recommendation: For patients with GPA whose disease has entered remission, we conditionally recommend treatment with methotrexate or azathioprine over trimethoprim/sulfamethoxazole for remission maintenance.

The Voting Panel strongly favored the use of methotrexate or azathioprine over trimethoprim/sulfamethoxazole, but this recommendation is conditional due to the lack of sufficient high-quality evidence comparing the 2 treatments.

Recommendation: In patients with GPA whose disease has entered remission, we conditionally recommend *against* adding trimethoprim/sulfamethoxazole to other therapies (e.g., rituximab, azathioprine, methotrexate, etc.) for the purpose of remission maintenance.

Trimethoprim/sulfamethoxazole may have benefit for patients with sinonasal involvement (25), but its use potentially increases toxicity (e.g., severe hypersensitivity reactions) and medication burden. Trimethoprim/sulfamethoxazole may still be indicated for prophylaxis against *P jirovecii* pneumonia (see GPA/MPA recommendation on this topic). There is a potential drug interaction between methotrexate and trimethoprim/sulfamethoxazole when trimethoprim/sulfamethoxazole is dosed at 800 mg/160 mg twice a day. The trimethoprim/sulfamethoxazole dose used for *Pneumocystis* prophylaxis is generally tolerated, but its use should be monitored when used in conjunction with methotrexate.

Recommendation: For patients with GPA/MPA receiving remission maintenance therapy with rituximab who have hypogammaglobulinemia (e.g., IgG <3 gm/liter) and recurrent severe infections, we conditionally recommend immunoglobulin supplementation.

Immunoglobulin supplementation at replacement doses (e.g., 400–800 mg/kg/month) should be considered if a patient has hypogammaglobulinemia and is experiencing recurrent infections. Immunoglobulin supplementation can also be considered for patients with hypogammaglobulinemia without recurrent infections but with impaired vaccine responses (26). These considerations should be made in collaboration with an allergist/immunologist.

Ungraded position statement: The duration of nonglucocorticoid remission maintenance therapy in GPA/MPA should be guided by the patient's clinical condition, preferences, and values.

The optimal duration of remission maintenance therapy is not well established. Although clinical trials have typically administered remission maintenance therapy for ≥18 months, patients may benefit from continuing remission maintenance therapy for a longer duration (27). The Patient Panel favored remission maintenance therapy for ≥18 months and potentially longer depending on patient-specific factors. Factors to be considered include previous relapse history, extent of organ involvement, and disease characteristics such as ANCA status (with PR3-ANCA–positive patients more likely to experience disease relapse [28]).

Ungraded position statement: The duration of glucocorticoid therapy for GPA/MPA should be guided by the patient's clinical condition, preferences, and values.

The optimal duration of glucocorticoid therapy for GPA/MPA is not well established. The immunosuppressive effects of glucocorticoids contributing to disease control should be balanced with the toxicities associated with its use. Overall, patients expressed a desire to minimize the glucocorticoid dose as much as possible but recognized that some patients may require low-dose glucocorticoids long-term to maintain disease quiescence. Screening for toxicities of glucocorticoid use (e.g., bone mineral density testing for osteoporosis) should be conducted.

Treatment of disease relapse

Recommendation: For patients with GPA/MPA who have experienced relapse with severe disease manifestations and are not receiving rituximab for remission maintenance, we conditionally recommend treatment with rituximab over cyclophosphamide for remission re-induction.

Rituximab is more effective than oral cyclophosphamide for re-induction of remission among patients who previously received cyclophosphamide and then experienced relapse, based on subgroup analysis of a randomized controlled trial (9). In addition, the cumulative toxicity of cyclophosphamide raises concerns over repeated use of this agent.

Recommendation: For patients with GPA/MPA who experienced relapse with severe disease manifestations while receiving rituximab for remission maintenance, we conditionally recommend switching from rituximab to cyclophosphamide over receiving additional rituximab for remission re-induction.

Multiple factors can influence whether rituximab or cyclophosphamide treatment (IV or oral) is used, such as time since last rituximab infusion and cumulative cyclophosphamide dose. Cyclophosphamide is recommended if the patient recently received rituximab, while a remission induction dose of rituximab may be

effective if an extended period has passed since the last rituximab infusion. As is standard for remission induction, these agents should be used in conjunction with glucocorticoids.

Treatment of refractory disease

Recommendation: For patients with severe GPA/MPA that is refractory to treatment with rituximab or cyclophosphamide for remission induction, we conditionally recommend switching treatment to the other therapy over combining the 2 therapies.

Disease refractory to remission induction therapy is rare, and there are limited data to guide treatment recommendations. Practitioners should evaluate whether other conditions such as infection could be mimicking vasculitis. However, if a patient's disease is refractory to one remission induction therapy, it is important to change the remission induction strategy. We recommend switching to the other remission induction agent prior to using combination therapy.

Recommendation: For patients with GPA/MPA that is refractory to remission induction therapy, we conditionally recommend adding IV immunoglobulin (IVIG) to current therapy.

IVIG should not be used routinely to treat GPA/MPA but can be considered at certain treatment doses (e.g., 2 gm/kg) as adjunctive therapy for short-term control, while waiting for remission induction therapy (i.e., rituximab or cyclophosphamide) to become effective (see above recommendation) (29).

Treatment of sinonasal, airway, and mass lesions

Ungraded position statement: For patients with sinonasal involvement in GPA, nasal rinses and topical nasal therapies (antibiotics, lubricants, and glucocorticoids) may be beneficial.

We suggest collaborating with an otolaryngologist with expertise in treating GPA to determine whether these interventions should be used.

Recommendation: For patients with GPA in remission who have nasal septal defects and/or nasal bridge collapse, we conditionally recommend reconstructive surgery, if desired by the patient.

To optimize surgical outcomes, reconstructive surgery should be performed, after a period of sustained remission, by an otolaryngologist with expertise in treating GPA (30,31).

Recommendation: For patients with GPA and actively inflamed subglottic and/or endobronchial tissue with stenosis, we conditionally recommend treating with immunosuppressive therapy over surgical dilation with intralesional glucocorticoid injection alone.

Subglottic or endobronchial stenoses should be managed by an otolaryngologist or pulmonologist, respectively, with expertise in management of these lesions. Immunosuppressive therapy is recommended for initial treatment of active inflammatory stenoses and usually comprises glucocorticoids and other agents (32); the degree of immunosuppressive therapy utilized may be based on the severity of other disease manifestations. Surgical dilation with intralesional glucocorticoid injection may be more appropriate for stenoses that are longstanding, fibrotic, or unresponsive to immunosuppression (32–34). Surgical dilation with intralesional glucocorticoid injection concurrent with medical treatment may also be considered as initial therapy for stenoses that require immediate intervention (e.g., critical narrowing).

Recommendation: For patients with GPA and mass lesions (e.g., orbital pseudotumor or masses of the parotid glands, brain, or lungs), we conditionally recommend treatment with immunosuppressive therapy over surgical removal of the mass lesion with immunosuppressive therapy.

Immunosuppressive therapy (with remission induction followed by remission maintenance) is almost always the initial treatment of choice for mass lesions (35,36). While these lesions tend to respond primarily to glucocorticoids, other agents are also usually used in hopes of having a glucocorticoid-sparing effect. Debulking surgery may be considered if there is an urgent need for decompression, such as acute visual loss due to optic nerve compression, or other life- or organ-threatening compression.

Other considerations

Recommendation: In patients with GPA/MPA, we conditionally recommend *against* dosing immunosuppressive therapy based on ANCA titer results alone.

Increases in ANCA titers/levels are only modestly informative as an indicator of disease activity (37) and are not reliable predictors of disease flares for individual patients. Increasing immunosuppressive therapy based on changes in ANCA titers/levels alone can result in unnecessary immunosuppression resulting in adverse events. Persistence of ANCA positivity does not necessarily indicate that continued immunosuppressive therapy is required. Instead, treatment decisions should be based on a patient's clinical symptoms in conjunction with diagnostic studies (e.g., laboratory, imaging, and biopsy findings).

Recommendation: For patients with GPA/MPA who are receiving rituximab or cyclophosphamide, we conditionally recommend prophylaxis to prevent *P jirovecii* pneumonia.

Prophylaxis to prevent *P jirovecii* pneumonia is routinely used with cyclophosphamide treatment (38). The prescribing information for rituximab recommends prophylaxis for *P jirovecii* pneumonia for ≥6 months after the last rituximab dose for patients with GPA or MPA. While many on the Voting Panel felt strongly that patients with GPA/MPA receiving cyclophosphamide or rituximab should receive prophylaxis against *P jirovecii* pneumonia, this recommendation is conditional given the lack of moderate-

Table 3. Recommendations/statements for the management of EGPA*

Recommendation/statement	PICO question informing recommendation and discussion	Level of evidence
Remission induction for active, severe disease		
Ungraded position statement: For patients with active, severe EGPA, either IV pulse GCs or high-dose oral GCs may be prescribed as initial therapy.	3	Very low
Ungraded position statement: For patients with active, severe EGPA, either cyclophosphamide or rituximab may be prescribed for remission induction.	4	Very low
Recommendation: For patients with active, severe EGPA, we conditionally recommend treatment with cyclophosphamide or rituximab over mepolizumab for remission induction.	6, 7	Low
Remission induction for active, nonsevere disease		
Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with mepolizumab and GCs over methotrexate, azathioprine, or mycophenolate mofetil and GCs.	8, 9, 10, 13	Very low to low
Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and GCs over GCs alone.	14	Low
Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and GCs over cyclophosphamide or rituximab and GCs.	11, 12	Very low to low
Remission maintenance		
Recommendation: For patients with severe EGPA whose disease has entered remission with cyclophosphamide therapy, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over rituximab for remission maintenance.	15, 16, 17,18	Very low
Recommendation: For patients with severe EGPA whose disease has entered remission, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over mepolizumab for remission maintenance.	20	Very low
Ungraded position statement: The duration of GC therapy in EGPA should be guided by the patient's clinical condition, values, and preferences.	21, 22, 23, 29, 30	Very low to low
Treatment of relapse		
Recommendation: For patients with EGPA who have experienced relapse with severe disease manifestations after prior successful remission induction with cyclophosphamide, we conditionally recommend treatment with rituximab over cyclophosphamide for remission re-induction.	25	Very low
Recommendation: For patients with EGPA who have experienced relapse with severe disease manifestations after prior successful remission induction with rituximab, we conditionally recommend treatment with rituximab over switching to cyclophosphamide for remission re-induction.	25	Very low
Recommendation: For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, we conditionally recommend adding mepolizumab over switching to another agent.	26	Very low
Recommendation: For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving low-dose GCs and no other therapy, we conditionally recommend adding mepolizumab over adding methotrexate, azathioprine, or mycophenolate mofetil.	28	Very low
Recommendation: For patients with EGPA and high serum IgE levels who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, we conditionally recommend adding mepolizumab over adding omalizumab.	27	Very low
Other considerations		
Recommendation: For patients with newly diagnosed EGPA receiving leukotriene inhibitors, we conditionally recommend continuing leukotriene inhibitors over discontinuing them.	33	Very low
Ungraded position statement: Use of leukotriene inhibitors is not contraindicated for patients with EGPA with active asthma and/or sinonasal disease.	34	Very low
Recommendation: For patients with EGPA, we conditionally recommend obtaining an echocardiogram at the time of diagnosis.	2	Very low
Recommendation: For patients with EGPA, we conditionally recommend using the Five-Factor Score to guide therapy.	1	Very low
Ungraded position statement: In patients with sinonasal involvement in EGPA, treatment with nasal rinses and topical therapies (e.g., antibiotics, lubricants, and GCs) may be considered.	31	Very low
Recommendation: For patients with EGPA who are receiving cyclophosphamide or rituximab, we conditionally recommend prescribing medications for prophylaxis to prevent *Pneumocystis jirovecii* pneumonia.	32	Low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for eosinophilic granulomatosis with polyangiitis (EGPA), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract). IV = intravenous; GCs = glucocorticoids.

or high-quality evidence directly addressing this question and the potential toxicity of the medications used for prophylaxis. Prophylaxis against *P jirovecii* pneumonia should also be considered for patients receiving moderate-dose glucocorticoids (e.g., >20 mg/day) or higher in combination with methotrexate, azathioprine, or mycophenolate mofetil (38). Prophylaxis

is less commonly used in younger children receiving rituximab but should be considered.

Recommendation: For patients with GPA/MPA in remission and stage 5 chronic kidney disease, we conditionally recommend evaluation for renal transplantation.

Outcomes of kidney transplantation in patients with AAV are similar to those in patients receiving transplants for other reasons, with disease relapses in the transplanted kidney being rare (39,40). GPA and MPA in remission should not be considered a contraindication to kidney transplantation, but these patients should be monitored for disease relapse after transplantation.

Recommendation: For patients with active GPA/MPA who are unable to receive other immunomodulatory therapy, we conditionally recommend administering IVIG.

IVIG should not be used routinely to treat GPA/MPA (see above recommendation). However, in the rare instances in which patients with active disease may not be able to receive conventional immunosuppressive therapy (e.g., sepsis or pregnancy), IVIG can be used as a short-term intervention until conventional remission induction therapies can be used (29).

Ungraded position statement: The optimal duration of anticoagulation is unknown for patients with GPA/MPA who experience venous thrombotic events.

AAV is associated with an increased risk of venous thrombotic events, including both deep vein thromboses and pulmonary emboli (41,42). Venous thromboembolic events that occur in a patient with active disease and no other risk factors can be considered a provoked event with a transient risk factor (assuming subsequent disease control). Thus, short-term instead of lifelong anticoagulation may be considered.

Recommendations and ungraded position statements for EGPA

EGPA is characterized by diverse features, including asthma/allergic rhinitis, peripheral and tissue eosinophilia, and vasculitis. As these clinical features can potentially have differing responses to treatment, the management approach is typically based on a patient's disease features and severity. The recommendations presented here focus primarily on the use of immunosuppressive medications to treat the vasculitic manifestations of EGPA. However, asthma and allergic manifestations are a significant component of EGPA, and measures directed toward these, including inhaled therapies and allergen avoidance, play an important role in management. Collaboration between rheumatologists, asthma/allergy specialists, and specialists in other medical disciplines can enhance the care of patients with EGPA.

In contrast to GPA/MPA, there have been very few randomized controlled trials conducted to date in EGPA. These recommendations and ungraded position statements therefore reflect reliance on lower-quality (i.e., indirect) evidence, including expert opinion.

Table 1 presents the definitions of selected terms used in the recommendations and ungraded position statements, including the definition of severe and nonsevere disease and the dosing regimens of medications used for remission induction and maintenance. Table 3 presents the recommendations and ungraded position statements with their supporting PICO questions and levels of evidence. Figure 2 presents key recommendations for the treatment of EGPA.

Remission induction for active, severe disease

Ungraded position statement: For patients with active, severe EGPA, either IV pulse glucocorticoids or high-dose oral glucocorticoids may be prescribed as initial therapy.

There are no data to support favoring either IV pulse or high-dose oral glucocorticoids over the other option in active, severe EGPA. Choosing an approach should be influenced by individual patient factors. In either instance, glucocorticoids should be combined with a nonglucocorticoid immunosuppressive agent such as cyclophosphamide or rituximab (see ungraded position statement below).

Ungraded position statement: For patients with active, severe EGPA, either cyclophosphamide or rituximab may be prescribed for remission induction.

Cyclophosphamide has been more commonly used for remission induction in patients with active, severe EGPA, given the experience with cyclophosphamide in other forms of vasculitis (43). Increasing experience with rituximab in GPA/MPA has also led to more patients with EGPA being treated with rituximab, and case series suggest that rituximab may also have efficacy for active, severe disease (44). Given that the comparative effectiveness of cyclophosphamide and rituximab for EGPA is unknown, the Voting Panel felt that both cyclophosphamide and rituximab could be considered for remission induction in active, severe EGPA. Cyclophosphamide would be preferred for patients with active cardiac involvement given the increased experience with cyclophosphamide, as cardiomyopathy has been found to be the main independent predictor of death in EGPA (25,26). Cyclophosphamide can also be considered for patients who are ANCA-negative and have severe neurologic or gastrointestinal manifestations. Rituximab may be considered for patients with positive ANCA results, active glomerulonephritis, prior cyclophosphamide treatment, or those at risk of gonadal toxicity from cyclophosphamide.

Recommendation: For patients with active, severe EGPA, we conditionally recommend treatment with cyclophosphamide or rituximab over mepolizumab for remission induction.

The efficacy of mepolizumab in severe EGPA has not been established, as patients with active, severe disease were excluded

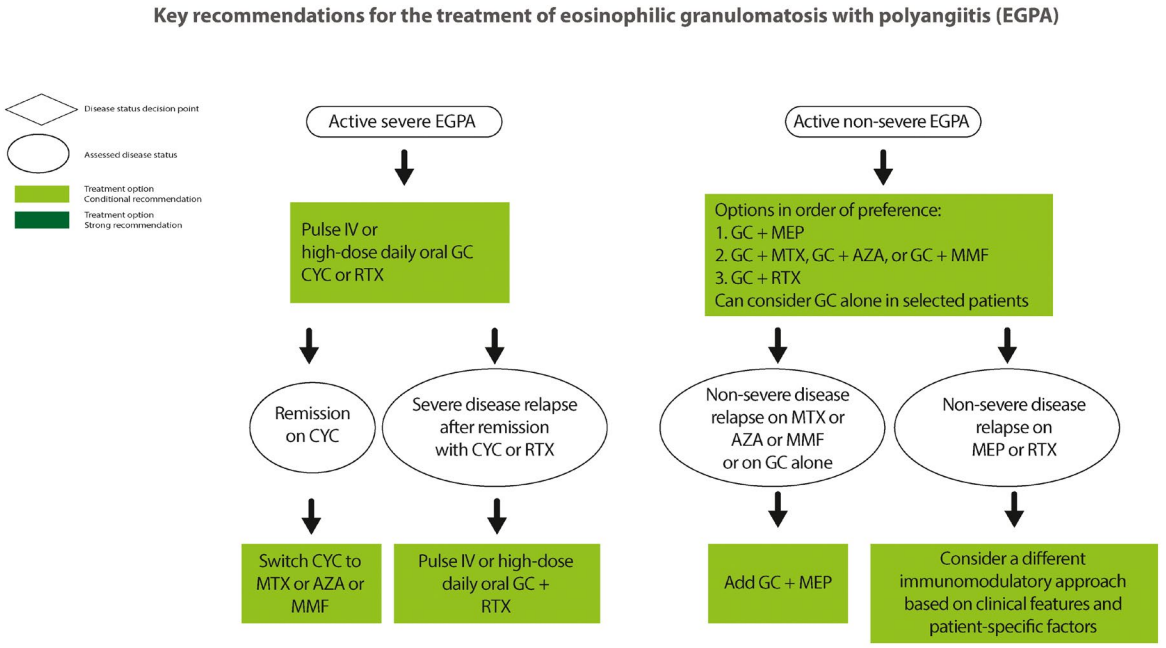


Figure 2. Key recommendations for the treatment of eosinophilic granulomatosis with polyangiitis.

from the randomized trial (45). Rituximab or cyclophosphamide is recommended over mepolizumab in this setting.

Remission induction for active, nonsevere disease

Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with mepolizumab and glucocorticoids over methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids.

A range of immunosuppressive agents may be considered in the treatment of active, nonsevere EGPA, all of which are used with glucocorticoids. The clinical profile of nonsevere EGPA includes predominantly asthma, sinus disease, and nonsevere vasculitis. While there is significant clinical experience with methotrexate, azathioprine, and mycophenolate mofetil, there are limited data regarding their efficacy, and these treatments have not been assessed in randomized clinical trials. The GRADE methodology used in the guideline development process weights clinical trials more heavily than observational studies. Thus, mepolizumab is recommended as the first choice, because it has been found to be efficacious for nonsevere EGPA in a randomized trial (45). All patients in this trial had relapsing or refractory disease, with 55% receiving an additional nonglucocorticoid immunosuppressive agent at the time of enrollment. A large proportion of patients in this trial had asthmatic and eosinophilic features, for which mepolizumab has also been found to be effective in non-EGPA disease settings. Although patients with nonsevere vasculitic manifestations were represented in this trial, questions remain about the effectiveness of mepolizumab for all aspects of nonsevere vasculitis. Individual factors, including disease manifestations, may impact the decision to use mepolizumab, in which case methotrexate, azathioprine, or mycophenolate mofetil may be used instead. There are insufficient data to favor one of these medications (methotrexate, azathioprine, or mycophenolate mofetil) over the others; therefore, the choice should be influenced by individual patient factors.

Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids over glucocorticoids alone.

Patients should be treated with adjunctive methotrexate, azathioprine, or mycophenolate mofetil rather than glucocorticoids alone in order to minimize glucocorticoid toxicity. One randomized trial that combined patients with EGPA, MPA, and polyarteritis nodosa without poor prognosis factors showed that the addition of azathioprine did not provide benefit beyond glucocorticoids alone (46). Particularly for patients with asthma, this may impact the decision to use methotrexate, azathioprine, or mycophenolate mofetil concurrently with glucocorticoids and could lead to consideration of mepolizumab. Glucocorticoid monotherapy may be appropriate for mild asthma, allergic symptoms, use during pregnancy, or other individual patient situations.

Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids over cyclophosphamide or rituximab and glucocorticoids.

While the comparative efficacy of methotrexate, azathioprine, mycophenolate mofetil, and rituximab is not well established, the use of methotrexate, azathioprine, or mycophenolate mofetil is favored, based on more experience with these agents in EGPA compared to rituximab. However, rituximab may be considered if other agents are not effective in controlling active, nonsevere disease, or if the patient has nonsevere vasculitis (which in some series included mononeuritis multiplex) and is positive for ANCA. Cyclophosphamide should be avoided when treating active, nonsevere disease due to its toxicity and is the least preferred option in this setting.

Remission maintenance

Recommendation: For patients with severe EGPA whose disease has entered remission with cyclophosphamide therapy, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over rituximab for remission maintenance.

Typically, a maintenance agent would be used after remission induction in severe EGPA to reduce toxicity and the risk of disease relapse (47), although monophasic disease can occur (48). Azathioprine has been commonly used in published EGPA series (46), but the lack of comparative evidence between methotrexate, azathioprine, and mycophenolate mofetil in EGPA precludes recommending one agent over another.

Use of methotrexate, azathioprine, or mycophenolate mofetil is recommended over rituximab, because there has been less experience with the use of rituximab for remission maintenance in EGPA. Rituximab could be considered if remission were induced with rituximab or if there are contraindications to other choices.

Recommendation: For patients with severe EGPA whose disease has entered remission, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over mepolizumab for remission maintenance.

While there are limited data informing the use of remission maintenance therapy in EGPA, remission induction therapies (e.g., cyclophosphamide) should not be indefinitely continued given the potential toxicity. Thus, methotrexate, azathioprine, or mycophenolate mofetil can be considered for remission maintenance based on experience in GPA/MPA, expert opinion, and results from small studies (49). The primary experience with mepolizumab is in refractory nonsevere disease, and thus it is difficult to extrapolate its efficacy as a remission maintenance agent for severe disease.

Ungraded position statement: The duration of glucocorticoid therapy in EGPA should be guided by the patient's clinical condition, values, and preferences.

There is insufficient published evidence to support a specific duration of glucocorticoid treatment, and thus, the length of glucocorticoid therapy should be determined based on each patient's clinical circumstances. Many patients with EGPA require some treatment with glucocorticoids, generally at a low dose, to maintain control of asthma and allergy symptoms. The minimum effective dose should be prescribed to minimize glucocorticoid toxicity.

Treatment of disease relapse

Recommendation: For patients with EGPA who have experienced relapse with severe disease manifestations after prior successful remission induction with cyclophosphamide, we conditionally recommend treatment with rituximab over cyclophosphamide for remission re-induction.

Rituximab is favored based on the general desire to avoid re-treatment with cyclophosphamide if possible and on the findings of an observational study of rituximab in relapsing or refractory EGPA (50). Cyclophosphamide may be considered in instances of recurrent cardiac involvement, since cardiac involvement is an independent predictor of death and is associated with ANCA-negative disease, as discussed in the ungraded position statement about remission induction in active, severe disease.

Recommendation: For patients with EGPA who have experienced relapse with severe disease manifestations after prior successful remission induction with rituximab, we conditionally recommend treatment with rituximab over switching to cyclophosphamide for remission re-induction.

Re-induction of remission with rituximab is favored over cyclophosphamide treatment to minimize toxicity. However, the duration of remission prior to the onset of relapse should be examined. Cyclophosphamide should be considered if a severe relapse occurred quickly after rituximab treatment, or if cardiac involvement is present (see ungraded position statement and recommendation on this topic).

Recommendation: For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, we conditionally recommend adding mepolizumab over switching to another agent.

For patients with EGPA with active asthma, inhaled therapies should be maximized prior to increasing systemic immunosuppressive therapy. Although no direct comparative

data are available, mepolizumab was found to be efficacious in a randomized trial in patients specifically described in this recommendation: those with relapsing nonsevere EGPA who are receiving immunosuppressive therapy (45). It has also been independently proven to be effective in eosinophilic asthma (51). Based on this evidence, mepolizumab is recommended to treat nonsevere relapsing disease in patients receiving methotrexate, azathioprine, or mycophenolate mofetil rather than switching to an alternative agent of that group.

Recommendation: For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving low-dose glucocorticoids and no other therapy, we conditionally recommend adding mepolizumab over adding methotrexate, azathioprine, or mycophenolate mofetil.

Similar to the discussion about the above recommendation, use of inhaled agents should be optimized in patients experiencing disease relapse with asthma and/or sinonasal disease. For patients with nonsevere relapsing EGPA who are receiving glucocorticoid monotherapy, starting mepolizumab would be preferred over adding methotrexate, azathioprine, or mycophenolate mofetil, given the treatment's proven efficacy in this population in a randomized trial (45).

Recommendation: For patients with EGPA and high serum IgE levels who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, we conditionally recommend adding mepolizumab over adding omalizumab.

The published evidence on omalizumab, an anti-IgE antibody, in EGPA has been limited. Therefore, even for a patient with high serum IgE levels, mepolizumab is the preferred choice based on evidence from the randomized controlled trial (45).

Other considerations

Recommendation: For patients with newly diagnosed EGPA receiving leukotriene inhibitors, we conditionally recommend continuing leukotriene inhibitors over discontinuing them.

Following the introduction of leukotriene inhibitors, concerns were raised about a link with the development of EGPA. In subsequent retrospective studies, it was not concluded that there is a causal relationship between leukotriene inhibitors and EGPA (52). Therefore, patients with newly diagnosed EGPA should have the option to continue a leukotriene inhibitor if it is beneficial in the management of their asthma or sinonasal disease.

Ungraded position statement: Use of leukotriene inhibitors is not contraindicated for patients with EGPA with active asthma and/or sinonasal disease.

Leukotriene inhibitors carry therapeutic indications for asthma and allergic rhinitis. As no clear causal association with EGPA has been demonstrated, a leukotriene inhibitor can be added to help manage asthma and sinonasal disease. However, leukotriene inhibitors are one of many options and are not the only choice in this setting. Leukotriene inhibitors should not be used to treat manifestations aside from asthma and sinonasal disease.

Recommendation: For patients with EGPA, we conditionally recommend obtaining an echocardiogram at the time of diagnosis.

Cardiac involvement is the major cause of disease-related mortality in EGPA (48). Echocardiography has minimal risk and can identify cardiac involvement, which, if present, can impact treatment decisions. Not identifying cardiac involvement could negatively impact patient outcomes. Thus, we recommend obtaining an echocardiogram for all patients with newly diagnosed EGPA, even in the absence of cardiac symptoms.

Recommendation: For patients with EGPA, we conditionally recommend using the Five-Factor Score to guide therapy.

The Five-Factor Score (FFS), first published in 1996 (53), was based on a cohort of 342 patients with either polyarteritis nodosa, as it was then defined, or EGPA. These 5 factors include proteinuria >1 gm/day, renal insufficiency with serum creatinine >1.58 mg/dl, gastrointestinal tract involvement, cardiomyopathy, and central nervous system involvement. The FFS is primarily a prognostic tool for which higher scores have been associated with a worse outcome (53). It has been used to guide treatment (43), but its applicability to newer therapies is unknown. The FFS was revisited in 2011 in a population of 1,108 patients with GPA, MPA, EGPA, or PAN (54). The 2011 version included ear, nose, and throat parameters and age >65 years. The 1996 FFS remains more commonly used and may be helpful in identifying organ-specific parameters associated with severe disease and in guiding treatment. Although the definitions of severe and nonsevere EGPA used in the present guideline were not based on the FFS, the tool was found to be useful to clinicians for making treatment decisions. The components of the FFS can serve as markers of severe disease that warrant more aggressive treatment.

Ungraded position statement: In patients with sinonasal involvement in EGPA, treatment with nasal rinses and topical therapies (e.g., antibiotics, lubricants, and glucocorticoids) may be considered.

Allergic rhinitis and sinonasal disease are frequent clinical features of EGPA. Although the efficacy of nasal rinses and topical

therapies in EGPA is not well established, some patients may benefit. Where possible, consultation with an otolaryngologist with expertise in treating AAV should be obtained to guide the use and choice of these agents. These interventions can continue to be beneficial even when symptoms have improved or resolved.

Recommendation: For patients with EGPA who are receiving cyclophosphamide or rituximab, we conditionally recommend prescribing medications for prophylaxis to prevent *P jirovecii* pneumonia.

Prophylaxis to prevent *P jirovecii* pneumonia is discussed above in the GPA/MPA recommendations. The same considerations regarding prophylaxis to prevent this condition in patients with GPA/MPA apply to those with EGPA.

DISCUSSION

In this guideline, we present the first ACR/Vasculitis Foundation recommendations for the management of GPA, MPA, and EGPA. Although these recommendations provide a general guide for disease management, the patient's clinical condition, preferences, and values should influence their treatment. Overall, these recommendations reflect the evolving management of these diseases, including the new roles for biologic therapies and aggressive strategies to minimize glucocorticoid toxicity. The recommendations for GPA and MPA are supported by a greater number of randomized trials than are currently available in EGPA. All of the recommendations made for these 3 diseases are conditional, which indicates that there are settings in which the evidence is not strong or an alternative is a reasonable consideration. These recommendations should not be used by any agency to restrict access to therapy or require that certain therapies be utilized prior to other therapies.

The physicians on the Voting Panel were primarily rheumatologists, because the recommendations were being developed for rheumatologists in the US. Since AAVs are multisystem diseases, patients with AAVs often receive care from other medical subspecialists (e.g., nephrologists, pulmonologists, and/or otolaryngologists). While the recommendations presented in this guideline are driven by the published data, other medical subspecialists may favor a different management strategy. We encourage rheumatologists to discuss treatment plans and coordinate care with other subspecialists as needed.

Recently, a clinical trial of avacopan in patients with GPA and MPA was published (55). This guideline development effort did not include consideration of avacopan, since the guidelines consider therapies that are approved by the FDA for use for any indication at the time of the last literature search. Therapies approved by the FDA after that date will be considered for inclusion in future updates to this guideline.

This guideline highlights gaps in our knowledge for the treatment of AAV. Most glaring is the lack of biomarker assessments or other noninvasive diagnostic testing with minimal toxicity that can accurately assess disease activity and predict outcomes. In addition, while we have evidence from randomized clinical trials to support recommendations regarding initial remission induction and maintenance therapy, critical questions remain unanswered, such as the optimal duration of therapy.

These gaps in knowledge reinforce the need for ongoing research in these diseases. Specific areas to investigate include the following: 1) biomarker studies to identify more specific, reliable indicators of disease activity that can guide treatment decisions; 2) trials to clarify how best to use the currently available medications (e.g., dosing, duration, effective combinations, and in which population to use which drugs); 3) trials to identify novel, targeted, and/or glucocorticoid-sparing agents with minimal toxicity; and 4) long-term studies to understand the course of disease and the safety of current therapies.

We hope significant progress will be made in these areas such that future recommendations provide a more tailored approach to disease management, minimize treatment toxicity, and prevent organ damage in these patients.

ACKNOWLEDGMENTS

We thank Anne M. Ferris, MBBS, Ora Gewurz-Singer, MD, Rula Hajj-Ali, MD, Eric Matteson, MD, MPH, Robert F. Spiera, MD, Linda Wagner-Weiner, MD, MS, and Kenneth J. Warrington, MD, for serving on the Expert Panel. We thank Antoine G. Sreih, MD, and Gary S. Hoffman, MD, MS, for their contributions during the early phases of this project as members of the Core Team. Dr. Hoffman's participation ended July 2018 due to personal reasons. Dr. Sreih's involvement ended in December 2018 when he became primarily employed by industry, which precluded his continued participation in this project. We thank Joyce Kullman (Vasculitis Foundation) for her assistance with recruitment for the Patient Panel. We thank the patients who (along with authors Kathy A. Full and Omar I. Vitobaldi) participated in the Patient Panel meeting: Jane Ascroft, Scott A. Brunton, Dedra DeMarco, Thomas Fitzpatrick, Jenn Gordon, Maria S. Mckay, Sandra Nye, Stephanie Sakson, and Ben Wilson. We thank Robin Arnold, Catherine E. Najem, MD, MSCE, and Amit Aakash Shah, MD, MPH, for their assistance with the literature review. We thank the ACR staff, including Ms Regina Parker, for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, and Ms Robin Lane for assistance in manuscript preparation. We thank Ms Janet Waters for help in developing the literature search strategy and performing the initial literature search, and Ms Janet Joyce for performing the update searches.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Chung and Langford had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Chung, Langford, Maz, Abril, Gorelik, Guyatt, Archer, Full, Grayson, Merkel, Seo, Stone, Sule, Sundel, Vitobaldi, Turner, Mustafa.

Acquisition of data. Chung, Langford, Maz, Abril, Gorelik, Full, Imundo, Kim, Merkel, Stone, Vitobaldi, Byram, Dua, Husainat, James, Kalot, Lin, Springer, Turgunbaev, Villa-Forte, Turner, Mustafa.

Analysis and interpretation of data. Chung, Langford, Maz, Abril, Gorelik, Archer, Conn, Full, Grayson, Ibarra, Imundo, Kim, Merkel, Rhee,

Seo, Stone, Vitobaldi, Warner, Byram, Dua, Husainat, Kalot, Lin, Springer, Turgunbaev, Mustafa.

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RHEUMATOLOGY

Rheumatology 2014;53:2306–2309
doi:10.1093/rheumatology/ket445
Advance Access publication 11 April 2014

Guidelines

BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis

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Key words: vasculitis, guideline, management, cyclophosphamide, rituximab.

GUIDELINES

Executive summary

Scope and purpose of the guideline

The ANCA-associated vasculitides (AAVs) are heterogeneous, multisystem disorders characterized by inflammation and necrosis of small and medium blood vessels with unknown aetiology. Three distinct clinico-pathological syndromes have been identified: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis and microscopic polyangiitis. The Chapel Hill Consensus Conference (CHCC) in 2012 updated the definitions, however, there are still no validated diagnostic criteria. The aim of this document is to provide guidelines for the management of adults with AAV.

The target audience is rheumatologists, nephrologists, general physicians, specialists, trainees and nurse practitioners. The guideline does not cover the management of other systemic vasculitides or the treatment of children.

This is a short summary of the guideline. The full guideline is available as supplementary material, available at *Rheumatology* Online. For definitions of levels of evidence and recommendation strength see Tables 1 and 2.

Guideline for the management of adults with AAV

We have produced evidence-based recommendations for treatment, giving a grade of recommendation (from A to D) and an algorithm to illustrate the approach to the management of a patient with newly diagnosed AAV.

NICE has accredited the process used by the BSR to produce its guidance for the management of ANCA-associated vasculitis in adults. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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Submitted 1 August 2013; revised version accepted 15 November 2013.

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Table 1 Level of evidence

Category	Evidence
Ia	From meta-analysis of randomized controlled trials
Ib	From at least 1 randomized controlled trial
IIa	From at least 1 controlled study without randomization
IIb	From at least 1 type of quasi-experimental study
III	From descriptive studies, such as comparative studies, correlation studies, or case–control studies
IV	From expert committee reports or opinions and/or clinical experience of respected authorities

Table 2 Determination of recommendation strength

Strength	Directly based on
A	Category 1 evidence
B	Category 2 evidence or extrapolated recommendations from category 1 evidence
C	Category 3 evidence or extrapolated recommendations from category 1 or 2 evidence
D	Category 4 evidence or extrapolated recommendations from category 2 or 3 evidence

Eligibility criteria

Patients with disease consistent with the definitions of ANCA vasculitis as defined by the CHCC in 2012 are eligible for treatment and use of this guideline.

Exclusion criteria

For a diagnosis of ANCA vasculitis, it is important to exclude other causes of systemic illness such as malignancy, systemic infection, drugs, secondary vasculitides or mimics.

Definition of disease states

Remission: well-controlled disease.

(i) On drug remission: prednisolone dose $\leqslant$10 mg/day and a BVAS $\leqslant$1 for $\geqslant$6 months.
(ii) Drug-free remission: $\geqslant$6 months off all treatment for vasculitis.

Relapsing: disease that has been previously well controlled with or without drugs and has become active.

Minor relapse: increase of one or more new or worse minor items and no major BVAS items.

Major relapse: increase of one or more major BVAS item.

Refractory: progressive disease that is unresponsive to current therapy, i.e. remission is not achieved.

Treatment

All patients with AAV should be considered to have severe, potentially life- or organ-threatening disease. Treatment regimens are divided into induction, maintenance and long-term follow-up. Patients who relapse may require a further course of induction therapy (secondary).

The essential principles of management are

(i) Rapid diagnosis
(ii) Rapid initiation of treatment
(iii) Early induction of remission to prevent organ damage
(iv) Maintenance of remission with the aim of eventual drug withdrawal
(v) Prevention of drug toxicity

Primary induction of remission

All patients with newly diagnosed AAV should be assessed for treatment with glucocorticoids (GCs) and i.v. pulse cyclophosphamide (CYC) or rituximab (RTX) (A) (Fig. 1).

Cyclophosphamide

CYC should be given by i.v. pulses initially at 2-week intervals and then at 3-week intervals following the CYCLOPS trial regimen (A). The standard dose is 15 mg/kg, reduced for age and renal function. Because of the lower toxicity, the i.v. regimen is preferred (B). Each individual course of CYC should be $\geqslant$3 months and $\leqslant$6 months (B). Lifetime exposure to CYC should be $\leqslant$25 g since the long-term toxicity of CYC is determined by cumulative dose (C). Patients on CYC should be monitored regularly and the dose should be reduced if there is CYC-induced leucopenia/neutropenia (B). Patients intolerant to CYC can be effectively treated with RTX (B).

Rituximab

RTX is as effective as CYC for remission induction of previously untreated patients and is preferable when CYC avoidance is desirable, such as in young people at risk of infertility and those at high risk of infection (B). The licensed RTX dosing protocol is 375 mg/m^2/week for 4 weeks (B), however, 1 g repeated after 2 weeks is equally effective (C).

MTX and MMF

MTX (up to 25–30 mg/week) and MMF (up to 3 g/day) are alternative remission induction agents for patients with

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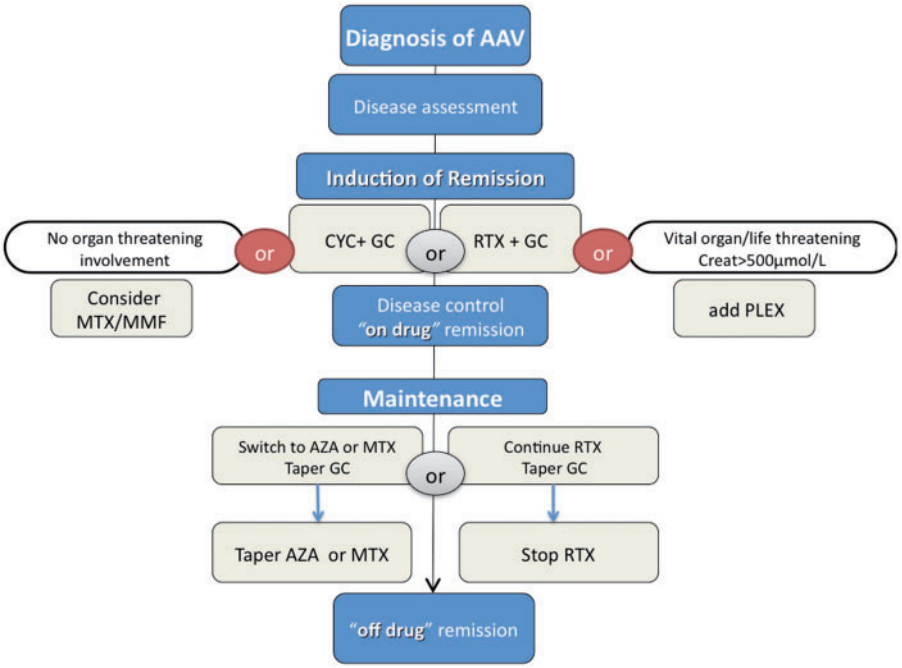
Fig. 1 Algorithm of the treatment guideline for AAV



evidence of low disease activity and not at risk of suffering organ damage as assessed by the BVAS (A). MTX should not be used in patients with moderate or severe renal impairment (B). MMF may be an alternative to MTX (B).

Plasma exchange

Patients with AAV presenting with severe renal failure (creatinine >500 μmol/l) should be treated with pulsed CYC and GCs, with adjuvant plasma exchange in a centre experienced in its use (B). Treatment with plasma exchange should also be considered in those with other life-threatening manifestations of disease, such as pulmonary haemorrhage (C).

Glucocorticoids

Induction therapy for AAV includes treatment with high-dose GCs in combination with another immunosuppressive agent (CYC, RTX) (A).

GCs are usually given as daily oral prednisolone, initially at relatively high doses (1 mg/kg up to 60 mg) (B) with the dose rapidly reduced to 15 mg prednisolone at 12 weeks (C). Longer courses of GCs may cause increased risk of infection, but may be associated with fewer relapses (A). GC i.v. infusions (250–500 mg methyl-prednisolone) are sometimes given just prior to or with the first two pulses of CYC (C).

Maintenance therapy

Following successful remission, CYC should be withdrawn and substituted with either AZA or MTX (A). MMF (C) or LEF (B) may be used as alternatives for intolerance to or lack of efficacy of AZA or MTX. Patients should continue maintenance therapy for at least 24 months following successful disease remission (B). Patients with GPA or patients who remain PR3-ANCA positive should continue immunosuppression for up to 5 years (C).

RTX may also be used as maintenance therapy, and re-treatment can be decided based on fixed-interval regimens or evidence of relapse (C). The recommended RTX regimen uses 1 g every 4–6 months for 2 years (B).

Withdrawal of treatment

Patients in continual remission for at least 1 year on maintenance therapy should be considered for tapering of GC treatment (D).

Following GC withdrawal, other immunosuppressive therapy may be withdrawn after 6 months (D).

Relapsing disease

Relapsing disease should be treated with an increase in immunosuppression. A minor relapse may be treated with an increase in prednisolone dosage and optimization of concurrent immunosuppression (C). A major relapse may be treated with RTX (A) or CYC with an increase in prednisolone (B). The addition of i.v. methylprednisolone or plasma exchange may also be considered (C). Drivers for relapse need to be identified and addressed and may include infection, malignancy and change of drug therapy (D).

Refractory disease

Refractory disease should only be treated in close collaboration with expert/tertiary centres via a hub-and-spoke

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model (D). RTX is more effective than CYC in refractory AAV (A). If the patient has not had previous treatment with RTX, then the first choice is RTX (A). Drivers for refractory disease should be sought and clinicians should consider revision of the clinical diagnosis (D).

Assessment and monitoring of disease status

Validated tools [such as the BVAS, Vasculitis Damage Index (VDI) and 36-item Short Form (SF-36)] should be used by trained staff to assess disease activity, extent of damage and quality of life (D). ANCA should be detected using IIF with ELISA to confirm PR3 or MPO specificity (C) and checked at diagnosis, relapse, change of therapy, every 6 months while on treatment and annually while off treatment (B). Results should be available within 1 working day (D). Treatment should not be escalated solely on the basis of an increase in ANCA (B).

Detection and prevention of potential adverse effects of immunosuppressive therapy

The following recommendations should be considered for patients with AAV on immunosuppressive therapy:

(i) Routine blood test monitoring [full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs)] (C)
(ii) Regular urinalysis and mesna for protection against CYC-induced urothelial toxicity (C)
(iii) Serum immunoglobulin measurement before each cycle of RTX therapy (C)
(iv) Trimethoprim/sulfamethoxazole as prophylaxis against *Pneumocystis jiroveci* (B)
(v) Antifungal prophylaxis (C)
(vi) *Staphylococcal aureus* treatment with long-term nasal mupirocin (C)
(vii) Screening for cervical intraepithelial neoplasia (CIN) (female patients) (C)
(viii) Counselling about the possibility of infertility following CYC treatment (C)
(ix) Prophylaxis against osteoporosis where appropriate (A)
(x) Tuberculosis screening (C)
(xi) Vaccination against pneumococcal infection, influenza and hepatitis B (C)
(xii) Cardiovascular and thromboembolic risk assessment (C)

Patient involvement and education

Patients should receive ongoing, tailored education and information about AAV and be encouraged to engage in self-monitoring to improve treatment compliance and long-term outcomes (D). They should have access to information about alternative and complementary therapies that might provide symptomatic relief (D).

Overview of care, collaboration and access to specialist services

Patients with AAV should be managed by a nominated clinician within clinical networks linked with centres of expertise and other specialities within the local organization (D). People with a suspected diagnosis of systemic vasculitis should be rapidly assessed by a specialist physician with an expertise in vasculitis (D). Self-referral mechanisms should be in place for patients, enabling rapid access to a specialist when flaring occurs (D).

Vasculitis annual review, research, audit and registries

Patients with AAV require long-term follow-up and should be encouraged to take part in studies and registries (D). Their annual review should follow a structured format. Audits may need to be conducted on a collaborative basis and may be focused on service delivery and patient-specific areas.

Key quality standards

Rapid access to specialist physicians.
Access to multidisciplinary team.
Provision of personalized education about the disease and its effects.
Access to a full range of therapies.
Opportunity to participate in registries and research projects.

Disclosure statement: R.A.W. has acted as a consultant for Roche and Euro Nippon Kayaku and has received unit support in the form of sponsorships for departmental meetings from multiple providers. D.J. has acted as a consultant for Roche/Genentech, Genzyme, GSK, UCB and Vijorpharma and has received research grants from Roche/Genentech and Genzyme. D.D.C has acted as a consultant and has participated on advisory boards for GSK, Roche, TEVA and Bristol-Myers Squibb and has received fees for speakers' bureaus from GSK. M.V. received unit and/or research support from Roche UK, Chemocentryx and GSK. All other authors have declared no conflicts of interest.

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RHEUMATOLOGY

Rheumatology 2020;59:e1–e23
doi:10.1093/rheumatology/kez672
Advance Access publication 23 January 2020

Guideline

British Society for Rheumatology

British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis

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Key words: giant cell arteritis, temporal arteritis, large-vessel vasculitis, guidelines, investigations, diagnosis, treatment

NICE accredited
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NICE has accredited the process used by the BSR to produce its guideline on the diagnosis and treatment of giant cell arteritis. Accreditation is valid for 5 years from 29 May 2019. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation

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Submitted 11 November 2019; accepted 2 December 2019

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This guideline was developed in accordance with the British Society for Rheumatology's Guidelines Protocol.

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Introduction

Background

GCA is a large vessel vasculitis affecting older people, with the highest incidence among persons 70–79 years of age [1]. Due to forecasted demographic changes, it has been estimated that between 2014 and 2050, >3 million people will have been diagnosed with GCA in Europe, North America and Oceania [2].

In GCA there is inflammation within the walls of medium and large-sized arteries, with associated intimal hyperplasia [3]. The ischaemia to end organs results in characteristic clinical features such as jaw or limb claudication [4]. Visual loss or stroke may occur in GCA, attributed to vascular occlusion; most GCA-associated visual loss occurs prior to glucocorticoid treatment or shortly after treatment initiation, underlining the importance of immediate treatment if the disease is strongly suspected [5, 6]. The reported proportion of patients with visual loss in GCA varies depending on the GCA case-finding method and method of ascertainment of visual loss; for example, in a UK study recruiting from a rheumatology setting, 17% of 271 patients with GCA reported irreversible visual loss and 1% had stroke [7]. Headache, scalp tenderness, jaw claudication, visual loss and stroke are all classified as cranial manifestations of GCA [4]. In addition, inflammation of the aorta and/or its proximal branches is common in GCA; this is often called large vessel vasculitis outside the head and neck (LV-GCA) and may be asymptomatic or produce non-specific systemic symptoms, such as fever or weight loss. Vascular imaging in GCA demonstrates large vessel involvement, usually with some degree of aortitis, in up to 83% of cases [8]. This large vessel inflammation may lead to later development of vascular stenosis, aneurysm or dilatation, dissection or rupture [9]. A subset of patients with LV-GCA presents with symptoms of a systemic inflammatory syndrome, which can have features of PMR without the classic cranial clinical features of GCA [4]. The true prevalence of this is unknown, as vascular imaging is not routinely performed in PMR at presentation.

Need for the guideline

As GCA is considered a medical emergency, it is treated at the point of diagnosis by clinicians in primary and secondary care who have a wide variety of clinical backgrounds. It is therefore necessary to provide clear guidance about current best practice and the underlying evidence including areas of uncertainty.

Recent years have seen new evidence emerge regarding the diagnosis and treatment of GCA. For this reason, a major revision to the 2010 British Society for Rheumatology (BSR) guideline for the management of GCA [10] was required. We also broadened the remit of the previous guideline to include diagnostic imaging for GCA.

Objectives of the guideline

The objective is to provide guidance for clinicians in the diagnosis and treatment of GCA. The guideline is supported by evidence wherever some evidence exists and by expert consensus where current evidence alone cannot provide a definite answer. The patient population covered by the guideline includes those patients in whom GCA is suspected sufficiently strongly that a decision to initiate glucocorticoid treatment is made. The guideline is not limited to GCA-related temporal (cranial) arteritis but also includes patients presenting with LV-GCA and limited forms of GCA with or without an association with PMR.

The evidence search was restricted to adult humans with GCA or suspected GCA, not limited by ethnicity, age or sex; however, since GCA is extremely rare in patients <50 years of age [1], generalizability below this age limit cannot be assured.

Areas the guideline does not cover

Takayasu arteritis and other forms of vasculitis (e.g. secondary large vessel vasculitis) are not covered by this guideline. The treatment of uncomplicated PMR is outside the scope of this guideline; readers are referred to the most recent BSR and ACR/EULAR guidance on the management of PMR [11, 12]. Guidance regarding immunizations and prophylaxis of glucocorticoid-induced osteoporosis is available elsewhere [13, 14].

Target audience

This guideline is intended for doctors and allied health professionals who work in a primary or secondary care setting and manage patients with suspected and/or established GCA. From a diagnostic perspective, early recognition of suspected GCA by the non-specialist is encouraged, but definitive diagnosis of GCA can be challenging and therefore prompt onward referral to an appropriate specialist is recommended. From a treatment perspective, this guideline is intended to provide a framework by which specialists, general practitioners and patients can work together to deliver optimal care tailored to the individual patient.

Stakeholder involvement

The guideline was developed in accordance with the BSR Guidelines Protocol. Members of the working group co-authored this guideline and are listed at the end of this document with their affiliations. Important stakeholder representation included patient groups (PMRGCAuk, PMR and GCA North East, PMR-GCA Scotland) and the Royal College of Ophthalmology. Individuals on the working group had a range of expertise, including rheumatology, general practice, ophthalmology, specialist rheumatology nursing and systematic review and guideline development methodology, and included patients with personal experience with GCA. There was no representation from industry. Informal feedback was sought at open meetings held at several international rheumatology conferences to ensure that the guideline development process took account of

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current practice and important clinical questions within the wider rheumatology community, particularly regarding general principles of management.

Prior to defining the Population, Intervention, Comparator, Outcome (PICO) questions, stakeholders were consulted regarding outcomes of importance in GCA [15]. A list of candidate outcomes was identified after feedback from all the stakeholders and from a scoping literature review. A survey was undertaken to prioritize candidate outcomes. A total of 67 patients, 45 rheumatologists, 10 generalists (general practitioners or hospital based) and 7 ophthalmologists responded to the questionnaire. Each outcome was graded based on its relative importance for clinical decision making on a 1–9 point scale [15]. Scores from 1–3 indicated limited importance (not important for decision making), 4–6 indicated important (important, but not critical for decision making) and 7–9 indicated critical (critical for decision making). Outcomes deemed as critical (i.e. score $\geq$7) by at least 70% of physicians and/or patients were considered as candidate outcome measures and this list was refined by the guideline working group for the purpose of defining a list of 'outcomes' for the PICO questions (Supplementary Files, available at *Rheumatology* online).

The GCA Guideline Working Group developed the PICO questions, discussed the evidence collated, iteratively refined the wording of draft recommendations and voted on the final recommendations.

Rigour of development

Scope of literature search and strategy employed

PICO questions

The systematic literature review (SLR) was directed according to predefined questions in PICO. These were written by the working group and feedback was explicitly invited from the patients within the group. The PICO questions were structured as follows:

1. For recommendations on diagnostic imaging tests, the (P) target population comprises patients with suspected GCA, the (I) intervention is the diagnostic test of interest, the (C) comparator is the comparator test or the reference standard and the (O) outcomes are true positives, true negatives, false positives, false negatives, complications related to tests, resource use, inconclusive results and the implication of these items on patient-important outcomes as listed below [16].
2. For recommendations on treatment, the (P) target population comprises patients with a diagnosis of GCA/patients with a high suspicion of GCA above the treatment threshold, (I) intervention and (C) comparator are the alternative management strategies and (O) outcomes as listed below [16].
3. For prognostic factors, the (P) target population comprises patients with a diagnosis of GCA, (I) the presence and (C) the absence of a prognostic factor and (O) outcomes as listed below [17].

A preliminary list of PICO questions was identified by a face-to-face discussion at the first guideline development group meeting followed by an e-mail-based survey of the working group. These preliminary questions were refined and grouped together where appropriate at the second guideline development group meeting. This resulted in a final list of PICO questions (Supplementary Files, available at *Rheumatology* online).

The PICO questions were used to formulate a protocol for the SLR, which was approved by BSR before commencing searches. Screening of the search output was performed by two group members for each topic (diagnostic tests: C. Duftner, S. Appenzeller; therapeutic strategies: C. Dejaco, D. Camellino; prognostic factors: S. Gonzalez-Chiappe, A.W. de Souza) who independently selected full texts, extracted data and performed quality appraisal. Any disagreements between the two group members were resolved by discussion, consulting a third member (S. Mackie, A. Hutchings or A. Mahr, respectively) when no consensus could be reached. The literature search was last updated on 18 June 2018 by G. Reynolds and the outputs appraised by the same group members as before for consistency.

The search strategy of electronic databases is given in the Supplementary Files, available at *Rheumatology* online. Further published studies were identified by hand-searching the reference list of full and review articles and by contacting experts in the field. In addition to this, ClinicalTrials.gov, ISRCTN and the European Union Clinical Trials Register were searched and the literature tracked to identify published trial results. Criteria for selecting articles for full-text review are given below.

Diagnostic studies

We included full research articles of prospective studies involving $>$20 patients and investigating the index test in patients with suspected GCA. We did not evaluate temporal artery biopsy as an index test because of incorporation bias in relation to the reference standard. We excluded diagnostic case–control studies because this type of study design produces estimates of diagnostic accuracy that are not applicable to routine clinical practice [18]; studies where the index (imaging) test had been performed in $>$10% of patients upon treatment with glucocorticoids for $>$1 week (because imaging tests for GCA suffer significant loss of sensitivity after commencing high-dose glucocorticoids; having an imaging test within 1 week of initiating glucocorticoids appears feasible in practice [19]); studies with a reference standard other than clinical diagnosis (without formal criteria), ACR classification criteria and/or temporal artery biopsy result and studies that could not be assigned to any of the PICO questions.

Interventional studies

We included randomized controlled trials (RCTs) involving $>$20 patients with GCA. Observational or non-randomized studies or studies that could not be

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assigned to any of the interventional PICO questions were excluded.

Prognostic studies

We included prospective and retrospective studies on >100 GCA patients investigating primarily the relevance of any of the prognostic factors of interest. Studies with another research focus (e.g. description of a cohort, interventional trials) were excluded for this part of the SLR. We further excluded studies that did not report the result of a statistical test for association with the outcome. The prognostic factors being investigated should have been in routine clinical use without requiring sophisticated equipment or complex analysis. A minimum time for follow-up in eligible studies was set at 6 months. Because the aim of this part of the SLR was to identify factors that could be used to risk-stratify patients in routine clinical practice, studies that reported exclusively on imaging or laboratory tests with no reference to patient presentation were excluded.

Data extraction

Study details and results were extracted using a data extraction form from included articles by two members of the literature review team according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [20]. The preliminary data extraction form was piloted in five identified articles and evaluated for completeness and handling. This data extraction form included the following items: authorship and publication, design, main study population, primary study objective(s), links/overlap with other studies, study inclusion criteria, characteristics of participants, definition of intervention/exposure and control, definition of outcome, method of statistical analysis, length of follow-up, losses to follow-up, missing data, discrete/continuous data (counts, means, standard deviations etc.), measures of effect and uncertainty and any other information relevant to quality assessment.

Additional parameters extracted relevant to diagnostic studies included the use of glucocorticoids before performance of imaging, disease characteristics [number (%) of patients fulfilling clinical criteria for GCA, number (%) of patients with positive temporal artery biopsy, number (%) of patients with large vessel GCA], technical aspects (imaging devices used, elementary lesions and structures investigated, blinding of the index test to a reference standard), index test, reference standard, diagnostic performance [raw data to calculate sensitivity, specificity, positive (LR+) and negative likelihood ratio (LR−)] and parameters required for assessment of study quality (risk of bias). Additional data extracted relevant to prognostic factors included adjusted and unadjusted odds ratios (ORs), relative risks (RRs) or hazard ratios (HRs) and information relevant to quality assessment.

Quality assessment

We evaluated the quality of evidence using the approach set out by GRADE [20, 21] and implemented as follows:

1. Risk of bias: Confidence in the estimate of the effect decreases if studies have major limitations that may bias their results. For diagnostic studies, risk of bias was assessed using the QUADAS-2 tool [22]. For interventional studies, the following factors were considered [20]: randomization procedure and sequence generation, allocation concealment, blinding of patients and assessor, completeness of outcome reporting (attrition bias: losses of follow-up, adherence to the intention-to-treat analysis or stopping the trial early for benefit) and selective outcome reporting. For prognostic studies, risk of bias was investigated using the following questions [17]:
   - Was there a representative and well-defined sample of patients? Was selection bias avoided?
   - Was follow-up sufficiently long and complete?
   - Were objective and unbiased outcome criteria used? Were methods used to determine/measure outcomes adequate?
   - Were all characteristics of patients known or suspected to affect the outcome recorded?
   - Was there adjustment for important prognostic factors, including age, sex, ESR, ischaemic manifestations (amaurosis fugax, jaw claudication, limb claudication), extracranial manifestations, symptom duration, comorbidities, constitutional symptoms and smoking?
2. Inconsistency of results: Confidence in the estimate of the effect decreases if there is variability in results (heterogeneity) across studies and investigators fail to identify a plausible explanation.
3. Indirectness of the evidence: Confidence in the estimate of the effect decreases if there are differences between the population, intervention, comparator or outcome of interest and those included in the systematic review studies.
4. Imprecision: Confidence in the estimate of the effect decreases if the systematic review includes relatively few patients and few events and thus has wide confidence intervals and/or the extremes of the confidence intervals are close to the null effect.
5. Publication bias: Confidence in the estimate of the effect decreases if there is evidence that some studies were not reported.

Evidence generated from prospective diagnostic accuracy studies, RCTs and longitudinal cohort studies investigating prognostic factors started as high quality but was downgraded if any of the above limitations was present.

After assessing these five domains the overall quality of evidence (QoE) was assessed as:

1. High quality evidence [indicated by ++++ (A) – further research is very unlikely to change our confidence in the estimate of effect]

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2. Moderate quality [indicated by +++ (B) – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate]
3. Low quality [indicated by ++ (C) – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate]
4. Very low quality [indicated by + (D) – any estimate of effect is very uncertain]

Preparing the evidence report

Evidence tables were prepared by the literature review team for each PICO question using Review Manager (RevMan; Cochrane Collaboration, London, UK) and GRADE profiler (GRADEpro) software. The evidence profiles contained the following specific information:

Diagnostic studies

Diagnostic studies included direct outcomes (true positives, true negatives, false positives, false negatives, sensitivities and specificities; complications of the index test and of the reference standard; resource use), the number of studies and quality assessment related to each of these outcomes and the effect estimate (i.e. number of individuals classified per 1000 people) according to different pretest probabilities [low (<20%), intermediate (20–50%) and high (>50%) pretest probability].

Interventional studies

Interventional studies included benefits and harms for each outcome across studies, the assumed and corresponding risk for comparators and interventions (95% CI), the absolute and relative effect (95% CI), the number of participants/number of studies, the number needed to treat and the QoE, including quality factors for each critical and important outcome.

Prognostic studies

Prognostic studies included ORs, RRs or HRs as well as corresponding *P*-values, both unadjusted and (where available) adjusted for confounders. Results of quality appraisal were also reported.

Whenever possible, meta-analyses using fixed effects methods (interventional studies) or random effects methods (diagnostic, prognostic studies) were conducted to combine the results of studies for each PICO question.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $P < 0.1$ and an I^2 inconsistency statistic of >50% to indicate significant heterogeneity. Where significant clinical heterogeneity was present, analysis of individual studies and/or subanalyses investigating studies with comparable design and quality was conducted.

Methods used to formulate the recommendations

General principles statements

GRADE recommends that where certain principles of diagnosis and treatment of a disease are generally agreed upon by the medical community, these should be stated in terms of 'good practice statements' [23]. Here we call these 'general principles' and they are a description of generally accepted best medical practice as evidenced by consensus within our Guideline Working Group. They are not necessarily evidence-based, but form the clinical context within which the evidence-based recommendations should be understood.

General principles statements in relation to GCA were drafted and iteratively refined by means of multiple rounds of e-mail consultation within the guideline working group, including patient representatives, as well as wider consultation by presentation and discussion at international rheumatology meetings. The final versions were voted on by the working group and a consensus score generated for each statement, defined as the mean value of scores of all the individual working group members.

Forming guideline recommendations

Using the evidence profiles, recommendations were proposed for each key question according to the GRADE methodology [24]:

The GRADE system offers two grades of recommendations: 'strong' and 'conditional'.

This grade is determined by the QoE, balance between desirable and undesirable effects, values and preferences of patients and use of resources.

The evidence on prognostic factors was used to build subgroups of GCA patients with different risk profiles concerning patients' important outcomes rather than formulating individual recommendations on prognostic factors. Treatment recommendations have been tailored to these subgroups given that the trade-off between benefit and harm, values and preferences as well as consideration regarding resource use may vary according to the presence or absence of risk factors.

The recommendations process was conducted in two stages:

1. The quality of evidence was discussed at international meetings and webinars.
2. Recommendations were formulated that were iteratively refined via webinars and e-mail.

Finally, the working group voted by scoring each recommendation on a 0–10 scale. The consensus score was defined as the mean of all scores received.

The overall QoE for each recommendation was summarized using the GRADE QoE scale, as per the BSR Guidelines Protocol 2017.

Limits of search and search dates

The following electronic databases were searched from their inception dates, noted in parentheses, to the

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present: Ovid MEDLINE (1946), Embase (1988), Cochrane Central Register of Controlled Trials (1996) and Cochrane Systematic Reviews (1993). The search was last updated on 23 June 2018.

Because of the need for quality appraisal by a consistent team of reviewers, the search was limited to articles published in English.

When will the guideline be updated?

The guideline will be updated after 3 years; publication of a major new clinical trial may trigger a partial revision.

The guideline

Eligibility

- Patients with suspected GCA (for diagnostic tests)
- Patients with confirmed GCA (for treatment recommendations)

Exclusions

- Takayasu arteritis
- PMR (unless there is also a diagnosis of GCA)

General principles

General principles are not the same as evidence-based recommendations, but are presented here to summarize best practice.

How should suspected GCA be treated?

1. Patients in whom GCA is strongly suspected should be immediately treated with high-dose glucocorticoids. Consensus score: 9.61.

'Strongly suspected' GCA means that in the assessing clinician's judgement, GCA is a more likely explanation for the patient's symptoms than any other condition. The assessing clinician may take into account GCA symptoms, signs and laboratory tests (such as acute phase markers) [25, 26]. The risk of toxicity caused by short-term glucocorticoid treatment commenced in patients with initial strong suspicion of GCA but then diagnosed with an alternative condition is acceptably low as long as a full diagnostic evaluation is performed promptly and it is acknowledged that a suspicion of GCA is not the same as a diagnosis of GCA. For doses, see below.

How quickly should patients with suspected GCA be referred for evaluation?

2. GCA is a medical emergency. Each local healthcare organization should have information available to front-line clinicians, such as general practitioners and clinicians working in acute care, on how to refer patients with suspected GCA urgently for local specialist evaluation. Patients should be evaluated by a specialist ideally on the same working day if possible and in all cases within 3 working days. Consensus score: 9.17.

Rapid specialist evaluation is a key principle of management of GCA, therefore 'fast-track' referral pathways for urgent specialist evaluation of suspected GCA are beneficial. On suspicion of GCA, primary care providers should initiate glucocorticoids alongside an urgent referral to the local GCA pathway. In retrospective reports from centres that have set up fast-track referral pathways, initial diagnostic evaluation and treatment of patients with suspected GCA within 24 h of referral has been associated with a reduction in reported rates of GCA-related sight loss compared with conventional care pathways [27, 28]. In a prospective, multicentre UK study, clinical evaluation, vascular ultrasound and temporal artery biopsy were all undertaken within 1 week of commencing high-dose glucocorticoid therapy for suspected GCA [19]. The success of fast-track referral pathways depends on appropriate selection of patients for referral and therefore education of clinicians in primary and secondary care is crucial.

To whom should patients with suspected GCA be referred?

3. Patients with suspected GCA should be evaluated by a clinician with appropriate specialist expertise, usually a rheumatologist. Patients presenting with a history of new visual loss (transient or permanent) or double vision should be evaluated as soon as possible on the same calendar day by an ophthalmologist. Consensus score: 9.61.

The reason for needing a full, prompt diagnostic evaluation by a clinician with appropriate specialist expertise is that undiscerning use of high-dose glucocorticoids may mask other diseases and can complicate the diagnostic workup [12, 25]. Where the diagnosis is difficult, opinions from specialists from multiple disciplines can be of value. This includes the interpretation of specialized investigations for GCA and consideration of alternative diagnoses. Ophthalmological evaluation is essential where there is visual loss, of which there are various possible causes in GCA [29, 30].

What evaluations should be performed when starting treatment?

4. When starting glucocorticoids for suspected GCA, diagnostically relevant symptoms and signs should be documented. Blood should be taken for full blood count, CRP and ESR before or immediately after commencing high-dose glucocorticoids. If GCA is strongly suspected, the first dose of glucocorticoid can be given without waiting for laboratory results. Consensus score: 9.61.

Diagnostically relevant symptoms and signs of GCA include headache; scalp tenderness/hyperaesthesia; jaw or tongue claudication; temporal artery tenderness, nodularity or reduced pulsation; visual manifestations including diplopia or changes to colour vision; limb claudication; PMR (pain and stiffness of the shoulder and hip girdles) and fever, sweats or weight loss. Less commonly, patients may have carotidynia, audiovestibular symptoms, dry cough or indications of tongue or scalp ischaemia that may precede necrosis.

However, as none of the above-mentioned symptoms is entirely specific (or pathognomonic) for GCA, and many are very non-specific, each is of limited use if

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Table 1 A proposed list of clinical assessments that could be carried out at or near diagnosis of GCA

History and examination	Investigations
• Height and weight • Features of GCA relevant to prognosis: fever, sweats or weight loss; ischaemic manifestations (jaw claudication, tongue claudication) • Signs and symptoms indicating involvement of extracranial arteries, e.g. bruits, different blood pressures in the two arms and limb claudication • Ophthalmological evaluation for patients with transient or permanent visual loss or diplopia • History of comorbidities and medications that might predispose to glucocorticoid-related adverse effects, including infection, hypertension, diabetes, osteoporosis, low-trauma fracture, dyslipidaemia, peptic ulcer and psychiatric adverse effects • Features that may suggest an alternative diagnosis, e.g. neurological deficits, very severe constitutional symptoms or localised ear, nose and throat signs	• Measures of activity of GCA: laboratory markers of inflammation (CRP for all patients, plus either ESR or plasma viscosity) and full blood count (platelet count may be elevated in GCA) • Consider serum protein electrophoresis and urine Bence–Jones protein/serum free light chains if ESR elevated out of proportion to CRP • Baseline laboratory tests of major organ system function (plasma glucose, renal and liver function tests, calcium and alkaline phosphatase) • Screening tests for risk of serious infection[a] (may include urine dipstick, chest radiograph and tests for latent tuberculosis according to local or national protocol) • Screening tests for osteoporosis risk[a] (may include TSH, vitamin D, bone density test, DXA)

[a]Screening tests for infection and osteoporosis to be considered in light of relevant local and national guidelines. TSH, thyroid stimulating hormone; DXA, dual-energy X-ray absorptiometry.

taken in isolation [26], and the differential diagnosis must also be considered. GCA causes an elevation in platelet count, CRP and ESR. Plasma viscosity can be used where ESR is unavailable. These markers all decrease with glucocorticoid therapy, therefore all patients should have blood drawn prior to starting treatment, unless there is evidence of critical ischaemia such as visual loss or diplopia and no immediate access to phlebotomy.

What evaluations should be performed soon after starting treatment for GCA?

5. Patients treated for GCA should be evaluated for features of the disease relevant to the prognosis, such as clinical and laboratory features of a marked inflammatory response at diagnosis, ischaemic manifestations such as transient visual loss or jaw/tongue claudication and signs or symptoms indicating involvement of the aorta and its proximal branches, and for comorbidities relevant to treatment, such as diabetes mellitus, hypertension and bone fracture risk. Consensus score: 9.53.

Assessments to be performed in all patients with GCA are detailed in Table 1. As well as confirmatory tests for GCA (see Key Recommendation 1), alternative explanations for patients' symptoms should be considered, particularly if these confirmatory tests are negative. Factors relating to prognosis [risk factors (prognostic) PICO questions 1–6] were reviewed. Overall, insufficient evidence was found to be able to stratify patients with proven GCA to different management strategies on the basis of risk factors considered: age, sex, acute phase reactants, PMR status, large vessel involvement in GCA, atherosclerotic disease, glucocorticoid responsiveness or histological features of GCA. Nonetheless, these features remain important diagnostically and/or when assessing for risk of glucocorticoid-associated adverse effects.

Risk factors for visual loss: Studies reporting risk factors for permanent visual loss in GCA yield variable results. In a single-centre study of 339 consecutive biopsy-proven cases presenting over a 39-year period, in which clinical features were prospectively recorded by an internist in a 176-item structured questionnaire, 53 patients had permanent visual loss. In multivariable regression modelling, older age, history of transient visual loss and jaw claudication were independent predictors of visual loss, while fever and rheumatic symptoms were protective [31]. Similar findings were reported in an earlier retrospective study of irreversible cranial ischaemic complications in 200 patients, with transient diplopia also identified as a potential risk factor [32].

Hypertension and ischaemic heart disease were also identified as potential risk factors for cranial ischaemic complications in studies from Italy and Spain [33, 34]. In an international multicentre observational study reporting data from 433 GCA patients from 26 countries, 34 patients developed complete loss of vision in one or both eyes at 6 months. After adjusting for age and sex, the strongest risk factor for this was peripheral vascular disease recorded at baseline (the effect size was similar when restricting the case definition to biopsy-proven GCA) [35].

Risk factors for aortic aneurysms: Inflammation of the aorta is associated with subsequent development of aortic dilatation or aneurysm [36], and those GCA patients with dilatation of the subclavian arteries were found to be more likely to have subsequent aortic aneurysm than those with GCA-related subclavian stenosis [37]. Possible risk factors for aneurysm development in GCA are smoking, male sex, hypertension and pre-existing cardiovascular disease as well as inflammation of the aorta or its proximal branches [37–41]. However, the evidence about risk factors for aneurysm development in GCA is at present not sufficient to define high-

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risk subgroups to select GCA patient subgroups for aortic imaging.

Chest radiography involves minimal radiation exposure but is insensitive to early thoracic aortic aneurysms [42]. French recommendations suggest routine aortic imaging at GCA diagnosis and every 2–5 years thereafter [43]. However, aortic imaging as a routine screening test for all GCA patients remains of uncertain cost-effectiveness and the optimal method and timing of imaging in this context is still unclear [44]. Therefore clinicians are advised to use their own discretion regarding selection of patients for aortic imaging.

Risk factors for prolonged treatment course: A 'strong inflammatory response' (defined as three or four of the following features: fever, weight loss, ESR $\geq$85 mm/h and haemoglobin $<$11 g/dl) has been associated with a higher relapse rate and prolonged treatment course [45–47]. Imaging evidence of LV-GCA may be associated with prolonged glucocorticoid treatment compared with patients with cranial GCA who did not have imaging evidence of LV-GCA [36, 48].

It is best practice for the prescriber of glucocorticoid therapy to ensure that patients are evaluated for hypertension and hyperglycaemia (blood glucose for acute changes and/or HbA1c to identify patients that might be at greater risk) within the first 2 weeks of commencing high-dose glucocorticoids. Comorbidities relevant to glucocorticoid toxicity include diabetes mellitus, osteoporosis and bone fracture. Generally, toxicity increases with glucocorticoid dose and duration [49]. Symptoms of and/or exposure to serious infections should be assessed in all patients starting glucocorticoids, considering the local prevalence of these infections. It is suggested that a chest radiograph and dipstick urinalysis should be performed. Exposure to tuberculosis should be discussed and screened according to national guidelines [50].

Oral glucocorticoids can rarely increase intraocular pressure or worsen pre-existing primary open-angle glaucoma. If there is glaucoma or ocular hypertension present, or a history of being a glaucoma suspect or glaucomatous risk factors (such as connective tissue disease, type I diabetes, a first-degree relative with primary open-angle glaucoma or high myopia), screening should be performed by a suitably trained eye professional [51].

For ongoing care via a shared care model, patients with GCA should see a clinician with appropriate expertise at least every 2–8 weeks during the first 6 months, then every 12 weeks during the second 6 months, every 12–24 weeks during the second year and additionally as indicated in case of relapse or as glucocorticoid therapy is tapered and discontinued. This visit schedule is based on the higher likelihood of new treatment-related adverse events and the need for treatment dose adjustment early in the treatment course while glucocorticoid doses are still high. However, this should be adapted for the individual patient. Each follow-up visit should include at least a full history, targeted physical examination and measurement of at least a full blood count, ESR and/or CRP, plus follow-up of any abnormalities relevant to the individual patient as well as drug-specific screening for toxicity.

How should ongoing management of GCA be individualized?

6. Full assessment of the disease and comorbidities and consideration of the patient's personal priorities should inform decisions about glucocorticoid tapering and initiation of additional treatments such as glucocorticoid-sparing therapies. Involvement of and clear communication with primary care physicians is critical, especially for management of multimorbidity. Consensus score: 9.67.

Management of patients with GCA should include attention to comorbidities and the impact of glucocorticoid toxicities in order to individualize the standard glucocorticoid tapering schedule (Table 2). PICO questions on the prevention of glucocorticoid-induced osteoporosis and immunization in GCA were not included; there are published guidelines on these matters [13, 14]. Although it is customary to co-prescribe proton pump inhibitors with high-dose glucocorticoid therapy, especially in older patients, it has recently been suggested that lower glucocorticoid doses may not always routinely need co-prescription of a proton pump inhibitor [53]. Local or national guidance should be followed.

Glucocorticoid therapy increases susceptibility to infections but may also decrease the efficacy of vaccinations; live vaccines are contraindicated in patients receiving high-dose glucocorticoid therapy ($>$20 mg prednisolone daily for $\geq$2 weeks) [54]. Patients without a history of chicken pox (varicella zoster virus infection) should be advised to avoid close contact with people who have chickenpox or shingles and to seek urgent medical advice if they have been exposed.

What education should patients be offered?

7. All patients with GCA should be provided with information about GCA and its treatment. Patients should receive advice on diet, physical activity and stopping smoking. Consensus score: 9.47.

Information should be available in written format and ideally in multiple formats. Dietary considerations include mitigating the potential effects of glucocorticoid therapy on body weight, post-prandial glycaemia and bone fracture risk. Recommendations on physical activity in inflammatory arthritis and osteoarthritis are available [55] and there have also been suggestions of benefit in other inflammatory vascular diseases [56], but advice needs to be tailored to the individual patient with GCA, particularly if there are comorbidities.

Particular considerations in GCA may include physical deconditioning as a result of the inflammatory disease, vascular stenosis to the limbs and the role of exercise in stimulating collateral formation and the psychological benefits of exercise in mitigating the impact of the disease on the patient. Particular considerations with patients receiving long-term glucocorticoid treatment

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Table 2 A typical glucocorticoid tapering schedule for GCA

Daily prednisolone dose	Example rate of reduction in daily prednisolone dose	Notes
40–60 mg oral prednisolone: initial dose for patients with active GCA	Continue at same dose until GCA symptoms and acute phase markers resolve	Purpose: induction of clinical remission
In clinical remission and >20 mg prednisolone	Reduce daily dose by 10 mg every 2 weeks	Aim to reach 20 mg prednisolone once the patient has been in remission for 4–8 weeks
In clinical remission, >10 mg prednisolone but <20 mg	Reduce daily dose by 2.5 mg every 2–4 weeks	If symptoms suggestive of GCA relapse occur during taper, consult Table 3
In clinical remission and on ≤10 mg prednisolone	Reduce daily dose by 1 mg every 1–2 months	

This is an example of a typical glucocorticoid taper schedule, based on that described in the 2010 BSR guidelines for GCA [10] and similar to the control arm of a recent GCA clinical trial [52]. High-quality evidence comparing different glucocorticoid taper schedules in GCA is not available. Alternative approaches include, for example, reducing prednisolone by 10 mg/week in patients who are in remission at >20 mg daily and/or reducing the dose slower than stated here in patients who are on ≤5 mg daily. In all cases, taper schedules should be individualized based on the patient. For relapse management, see Table 3.

Table 3 Examples of symptoms that may signify relapse of GCA during glucocorticoid taper that require further evaluation and, if judged to be due to GCA relapse, escalation of glucocorticoid treatment

Symptom	Possible significance in a patient with GCA	Action to consider if symptom is judged to be due to GCA relapse
Return of headache symptoms	Possible GCA relapse without ischaemic manifestations	Return to previous higher prednisolone dose
Jaw or tongue claudication	Possible GCA relapse with ischaemic manifestations	Consider high-dose oral prednisolone (40–60 mg) with or without glucocorticoid-sparing agent
Weight loss, fever, night sweats, anaemia, persistent acute phase response, new/recurrent PMR symptoms, limb claudication, abdominal pain or back pain	Possible GCA-related inflammation of the aorta and/or its proximal branches	Investigate with vascular imaging (MRI, CT or FDG-PET/CT); consider increasing oral prednisolone and/or adding glucocorticoid-sparing agent

This table outlines how new symptoms in GCA patients, in the absence of other risk factors or significant comorbidities, may influence management decisions. New visual loss or diplopia should be urgently evaluated by an ophthalmologist. Acute phase markers should be measured and, if found to be elevated, may increase the clinical suspicion of GCA relapse. At present, the only agents with any evidence for glucocorticoid-sparing in GCA are methotrexate and tocilizumab.

may include myopathy, which typically develops after weeks or months of glucocorticoid therapy (particularly at high doses); insulin resistance limiting the ability of skeletal muscle to take up glucose and store glycogen; bone fragility and central adiposity. Exercise can also be beneficial for improving balance and general mobility, which may be affected by alterations to vision and biomechanics.

The role of exercise programmes in GCA has not been formally evaluated in clinical studies. Patients should be signposted to relevant patient support groups or charities as sources of peer support. Patients should be advised of potential symptoms of glucocorticoid withdrawal, although these are uncommon in practice. Patients should be advised about alteration of their glucocorticoid dose in intercurrent illness, especially including advice for seeking emergency attention if they suffer a vomiting illness necessitating parenteral glucocorticoid.

What plans should be made for possible future GCA relapses?

8. During glucocorticoid taper and after glucocorticoid cessation, patients should be informed what symptoms may suggest GCA relapse and what action the patient should take in these circumstances, including the first point of contact for medical advice and how to contact the team providing specialist care. Consensus score: 9.81.

Examples of actions to consider if new GCA-attributable symptoms develop are given in Table 3.

Specific recommendations for diagnostic tests in suspected GCA

As affirmed in the 2010 BSR/British Health Professionals in Rheumatology guideline, there is an urgent need for confirmation of disease in every suspected case of GCA [10]. In the 2010 guidance, it was recommended that

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temporal artery biopsy was desirable in every case of suspected GCA. In this edition, this recommendation has been updated in view of new evidence regarding imaging tests for diagnosis of GCA.

Which additional confirmatory diagnostic tests should be performed in all patients with suspected GCA? (PICO 1, 2)

Diagnostic accuracy may be expressed as sensitivity and specificity, or as a likelihood ratio; this information can be combined with the pretest probability (established on clinical grounds) to select and interpret the results of confirmatory diagnostic tests. Compared with biopsy, imaging tests such as ultrasound have the advantage of access to both superficial temporal arteries in their entirety. Most diagnostic accuracy studies have focussed on the role of ultrasound ($n = 16$) or MRI ($n = 7$). One study addressed the role of FDG-PET and another study examined the role of FDG-PET and CT angiography (CTA) for GCA diagnosis.

Seven studies (519 patients with suspected GCA, of whom 169 were diagnosed with GCA) compared the ultrasound 'halo' sign with a clinical diagnosis of GCA, giving a pooled sensitivity of 79% (95% CI 73, 84) and pooled specificity of 94% (95% CI 90, 96) [57–63]. The QoE was +++; downgrading was performed because of risk of bias in four of seven studies. One of these studies included 12 patients with a final diagnosis of LV-GCA [58].

Five studies (185 patients with suspected GCA, of whom 57 were diagnosed with GCA) compared the ultrasound 'halo' sign with temporal artery biopsy, giving a pooled sensitivity of 74% (95% CI 63, 83) and pooled specificity of 81% (95% CI 73, 88) [61–65]. The QoE was +; downgrading was performed because of high risk of bias in all five studies and because of inconsistency. Patients with LV-GCA were not evaluated in these studies.

Two studies (140 patients with suspected GCA, of whom 67 were diagnosed with GCA) compared the ultrasound 'compression' sign of temporal arteries with ACR criteria–based diagnosis of GCA, giving a pooled sensitivity of 79% (95% CI 67, 88) and a pooled specificity of 100% (95% CI 95, 100) [57, 66]. The QoE was ++; downgrading was performed for risk of bias in one of the studies and because both studies were performed by the same research group. The ACR criteria for GCA, which are not suitable for clinical diagnosis, served as the reference standard in both studies.

Three studies (560 patients with suspected GCA, of whom 327 had a clinical diagnosis of GCA) compared the diagnostic performance of ultrasound abnormality (defined as any one of halo, stenosis or occlusion) with clinical diagnosis of GCA, giving a pooled sensitivity of 61% (95% CI 56, 67) and pooled specificity of 86% (95% CI 81, 90) [19, 63, 67]. The QoE was ++; downgrading was performed for risk of bias in all three studies and for inconsistency.

Four studies (563 patients with suspected GCA, of whom 180 had a positive temporal artery biopsy) compared the diagnostic performance of ultrasound abnormality (defined as any one of halo, stenosis or occlusion) with temporal artery biopsy, giving a pooled sensitivity of 81% (95% CI 74, 86) and pooled specificity of 74% (95% CI 70, 79) [19, 63, 67, 68]. The QoE was ++; downgrading was performed for risk of bias in three of the four studies and for imprecision.

Neither clinical diagnosis nor temporal artery biopsy are perfect reference standards for evaluating the diagnostic accuracy of ultrasound for GCA, because neither of these are themselves 100% accurate. Clinical diagnosis is based on clinical symptoms, signs and laboratory tests, each of which are imperfect markers for GCA.

A positive temporal artery biopsy showing features of inflammation characteristic of GCA such as giant cells or panarteritis [69] confirms the diagnosis of GCA. Although the true sensitivity of temporal artery biopsy is not precisely known, it is accepted that its sensitivity is substantially <100%; this is supported by the histological observation of skip lesions in some cases. An imperfect reference standard would result in underestimation of the diagnostic accuracy of ultrasound. When using clinical diagnosis as a reference standard it is important that this is made independently of the index test result in order to avoid bias. This may be done by blinding of the diagnostician to the index test result. Notably a large prospective UK study assessing the diagnostic value of ultrasound addressed this issue by blinding the patient, the treating clinician and the investigator to the ultrasound result [19].

Ultrasound was found to be more sensitive but less specific than biopsy for diagnosis of GCA, was cost effective and provided a method for reducing the number of patients who need a temporal artery biopsy [19]. Overall, the pooled positive and negative likelihood ratios for ultrasound appear to support its use either for ruling out GCA in low-probability cases or for confirming GCA in high-probability cases (Supplementary Files, available at *Rheumatology* online and Fig. 1). Ultrasound of the axillary arteries might add extra diagnostic information to ultrasound of the temporal arteries [70].

Six studies (500 patients with suspected GCA, of whom 268 were finally diagnosed with GCA) compared cranial artery MRI (vessel wall oedema and contrast enhancement) with clinical diagnosis, giving a pooled sensitivity of 75% (95% CI 69, 80) and a pooled specificity of 89% (95% CI 84, 93) [71–76]. The QoE was ++; downgrading was performed for risk of bias in five of the studies and because five of the six studies were performed by the same research group; sensitivity was somewhat lower in the study performed by a separate group [76].

Five studies (397 patients with suspected GCA, of whom 171 had positive temporal artery biopsy) compared cranial artery MRI (vessel wall oedema and contrast enhancement) with temporal artery biopsy, giving a pooled sensitivity of 94% (95% CI 90, 97) and specificity of 79% (95% CI 73, 84) [71–74, 76]. The QoE was +; downgrading was performed for risk of bias in five of the studies, for inconsistency and for likely publication bias.

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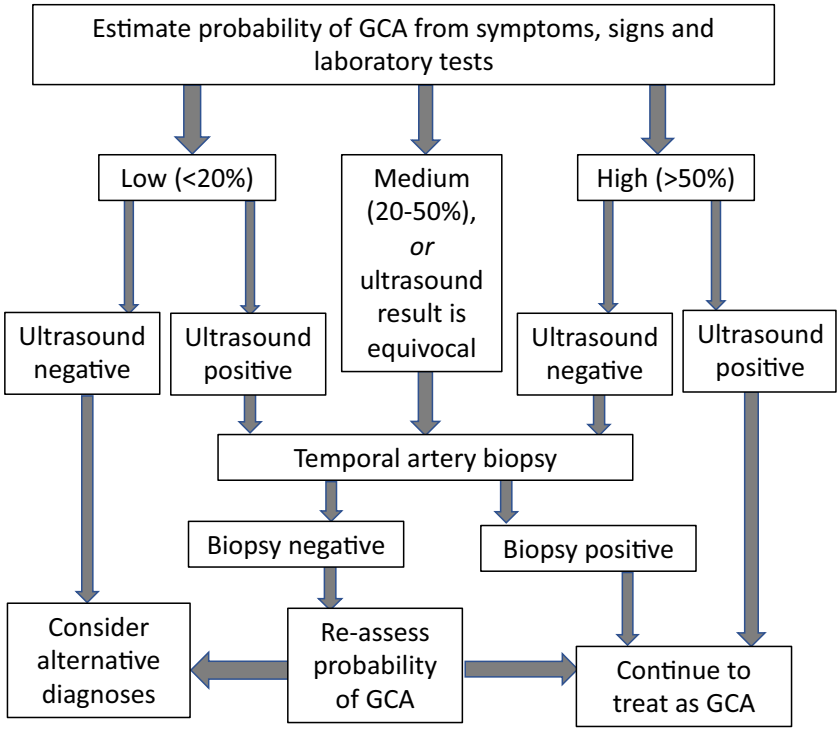
FIG. 1 A possible approach to using rapid-access vascular ultrasound to assist in clinical diagnostic decision making in suspected cranial GCA



This figure illustrates a possible approach to using rapid-access vascular ultrasound, if available, in suspected GCA. Estimation of the probability of GCA is based on all information available (symptoms, signs, laboratory tests and alternative non-GCA explanations for the clinical picture) and can be updated based on new information (clinical course, result of temporal and axillary ultrasound and/or results of temporal artery biopsy). This assessment is based on clinical judgement and should ideally be performed by an individual with specialist expertise. Note that for a medium (20–50%) estimated probability of GCA, it may be useful to perform an ultrasound prior to biopsy, in case the biopsy is negative. For a high clinical probability of GCA, a positive ultrasound alone may be sufficient, as illustrated here; however, in these cases it is still acceptable to perform biopsy in addition to ultrasound in order to further increase diagnostic certainty. In the absence of clinical features of cranial GCA, temporal artery biopsy can still be positive, but imaging of the extracranial large vessels may be considered instead of, or in addition to, temporal artery biopsy. Recently, various clinical prediction rules have been proposed to assist clinicians in the estimation of probability of GCA; the performance of a clinical prediction rule developed in another setting should ideally be checked using local audit data prior to adopting into local clinical practice. If rapid-access vascular ultrasound is not available, patients treated for suspected GCA should all have a temporal artery biopsy. None of these tests should delay the prescribing of high-dose glucocorticoid therapy for patients with strongly suspected GCA.

Overall, MRI of the cranial arteries appears to be potentially useful for ruling out GCA if the result is negative, but false-positive test results could occur, such that MRI of the cranial arteries would not be first choice for a confirmatory test in GCA [76]. Other issues of relevance to cranial vascular MRI are low availability of high-resolution 3T MRI equipment and expertise, higher costs and possible adverse effects of contrast agents.

In contrast to the 2010 guideline, where the authors outlined that imaging techniques are promising for diagnosis and monitoring of GCA [10], in this guideline there is now sufficient evidence, taken together, to state that all patients with GCA should have at least one confirmatory diagnostic test, which could be either temporal artery biopsy or temporal and axillary artery ultrasound. However, temporal artery biopsy and ultrasound differ in their positive and negative likelihood ratios for GCA, with biopsy having relatively greater 'rule-in' value and ultrasound having relatively greater 'rule-out' value (Supplementary Files, available at *Rheumatology* online). Selection of the most appropriate confirmatory diagnostic test(s) therefore requires an assessment of the pre-test probability as outlined elsewhere [77]; if both ultrasound and biopsy are possible, an approach to this is suggested in Fig. 1.

The ultrasound halo diminishes in size during the first week of glucocorticoid therapy, indicating that the sensitivity of the test is likely to depend on the delay between initiation of glucocorticoid therapy and the ultrasound test [19]. Ultrasound is operator-dependent and requires

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adequate training. Ultrasound performs best in the 'fast-track' setting, assuming rapid access, good technical equipment and high expertise with this method. With ultrasound, the non-compressible 'halo' sign is the most important finding suggesting GCA [78]. Temporal artery biopsy should be performed by a surgeon experienced in this procedure and samples should be at least 1 cm in length post-fixation. The pathologist evaluating the biopsy should be experienced in diagnosing GCA.

Data from the Temporal Artery Biopsy versus Ultrasound in the Diagnosis of Giant Cell Arteritis study [19] suggested significant variation between pathologists in the interpretation of temporal artery biopsy histology, so where biopsy findings are ambiguous (e.g. low-level inflammation restricted to the adventitia), discussion between the requesting clinician and the pathologist is desirable. In the absence of inflammatory infiltrate, a report of healed arteritis is not sufficient to diagnose GCA. Isolated vasa vasorum vasculitis is not diagnostic of GCA. Contralateral biopsy may slightly increase the yield of temporal artery biopsy, but is usually unnecessary. Biopsy may remain positive for several weeks after initiation of glucocorticoid therapy [79].

If neither vascular ultrasound nor biopsy is possible, and local MRI facilities and radiology support are available, then high-resolution 3T MRI of the cranial arteries could be used instead. In interpreting the results of these diagnostic tests, pretest probability (established on clinical grounds) should be taken into account (Fig. 1).

1. Strong recommendation: Patients with suspected GCA should have a confirmatory diagnostic test. This could be either a temporal artery biopsy at least 1 cm in length or an ultrasound of the temporal and axillary arteries, or both. QoE: +++. Consensus score: 9.33.

Which tests can be used to evaluate involvement of the aorta and its proximal branches in GCA? (PICO 2, 3)

One study (24 patients with suspected GCA, of whom 15 were diagnosed with GCA) compared FDG-PET with clinical diagnosis of GCA, giving a sensitivity of 67% (95% CI 38, 88) and a specificity of 100% (95% CI 66, 100) [80]. The QoE was ++; downgraded because of indirectness and publication bias.

One study (69 patients with suspected GCA/PMR, of whom 13 had biopsy evidence of GCA) compared vascular 18F-glucose uptake in the thorax and legs on FDG-PET with temporal artery biopsy, giving a sensitivity of 77% (95% CI 46, 95) and specificity of 66% (95% CI: 52%, 78%). Comparing vascular 18F-glucose uptake in the thorax on FDG-PET with temporal artery biopsy gave a sensitivity of 54% (95% CI 25, 81) and a specificity of 86% (95% CI 74,94). The QoE was +; downgraded because of risk of bias, indirectness and imprecision [81].

One study (24 patients with suspected GCA, of which 15 were diagnosed with GCA) compared CTA with clinical diagnosis of GCA, giving a sensitivity of 73% (95% CI 45, 92) and a specificity of 78% (95% CI 40, 97) [80]. The QoE was ++; downgraded for indirectness and publication bias. CTA can reveal wall thickening with contrast enhancement in biopsy-proven GCA [82]. There is also experience with CTA for accurate assessment of luminal diameter for large vessel stenosis in Takayasu arteritis [83].

No studies of magnetic resonance angiography (MRA) for the diagnosis of LV-GCA were found the met our criteria, but there is experience with MRI for the detection of vessel wall oedema reflective of inflammation and accurate assessment of luminal diameter for large vessel dilatation and stenosis in diseases of the major arteries, such as Takayasu arteritis. Gadolinium-enhanced MRA may help identify aortitis in the large vessel vasculitides, but appears to be very sensitive to glucocorticoid therapy [84].

In addition to showing inflammation of the large vessels, FDG-PET/CT may detect malignancy or infection and thus can be of use in the differential diagnosis of GCA. Contrast-enhanced CT of the chest and abdomen is also often used in clinical practice to screen for deep infection or occult malignancy. Moreover, aortic wall thickening on a contrast CT might help to identify GCA, albeit with lower sensitivity than FDG-PET/CT, and could also potentially have uses in settings where FDG-PET/CT is unavailable [80, 85, 86]. Additional advantages of FDG-PET and CT therefore include potential value in the workup of alternative diagnoses such as malignancy and infection.

As well as detecting axillary artery involvement for diagnosis of large vessel involvement in GCA, vascular ultrasound may also be able to visualize the carotid arteries and obtain more limited views of the subclavian arteries, vertebral arteries and parts of the aorta, but a higher level of operator expertise is required for these studies.

Overall, there is indirect evidence for the use of imaging tests to evaluate involvement of the aorta and its proximal branches in GCA, but the published evidence is extrapolated from other diseases such as Takayasu arteritis [77] and there is currently insufficient evidence from prospective studies of suspected GCA to yield precise estimates of diagnostic accuracy for these tests.

2. Conditional recommendation: 18F-FDG-PET, MRA, CTA or axillary artery ultrasound may be used to evaluate involvement of the aorta and its proximal branches. QoE: +. Consensus score: 9.36.

Recommendations for treatment of GCA

What is the best dose and route of initial glucocorticoid therapy for GCA in the absence of ischaemic visual manifestations? (PICO 1–3). There are no clinical trials comparing different initial oral glucocorticoid doses for GCA. However, clinical experience suggests that the vast majority of patients with GCA respond symptomatically within 1–7 days to a 40–60 mg daily dose of prednisolone, apart from irreversible sequelae such as established visual loss, stroke or tissue necrosis. Failure to respond to this dose should prompt re-evaluation of the diagnosis.

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In several clinical trials [87–89] the initial dose of oral prednisolone has been administered by weight rather than by a fixed dose, as is done for other systemic vasculitides in clinical practice. There was not enough direct evidence to be able to recommend dosing prednisolone strictly by weight, but nonetheless body weight (or at least size) remains a factor to be taken into account when deciding on an initial dose. Comorbidities also should be taken into account, since the toxicity of glucocorticoid therapy increases with the dose [49]. Clinicians should consider a higher dose within the 40–60 mg range for patients who have cranial ischaemic features of GCA such as ischaemic visual manifestations or jaw or tongue claudication, acknowledging that the evidence base for this is limited.

Two RCTs addressed the question of whether intravenous glucocorticoids should be given in patients with new-onset, uncomplicated GCA (i.e. those without any history of recent visual loss, amaurosis fugax or transient ischaemic attack): one was a single-centre, 78-week, double-blinded RCT ($n = 27$) and one was a 12-month open RCT ($n = 164$) [87, 90]. In the double-blinded RCT [90], patients received either 15 mg/kg body weight/day intravenous methylprednisolone for 3 days or placebo plus 40 mg/day oral prednisone. In the open RCT [87], the intervention group was treated with a single dose of 240 mg intravenous methylprednisolone followed by 0.7 mg/kg oral prednisone; one control group was treated with oral prednisone 0.7 mg/kg alone and a further control group was treated with a single dose of 240 mg intravenous methylprednisolone followed by 0.5 mg/kg oral prednisone. Due to the substantial differences in study design, efficacy outcomes were not meta-analysed. We pooled the data for treatment-related adverse events to increase the power to detect unwanted effects.

Moderate QoE (+++) from one study [90] suggested a reduction of the cumulative glucocorticoid dose at week 78 {median cumulative glucocorticoid dose 5636 mg [interquartile range (IQR) 4050–6690]} in the group that received 3 days of intravenous methylprednisolone compared with 7860 mg (IQR 7373–9005) in the control group. The glucocorticoid pulses were not counted for cumulative dose. In the other study, very low QoE (+) [87] indicated no benefit of pulse treatment at 1, 2, 6 and 12 months regarding cumulative glucocorticoid dose.

Low QoE (++) suggested that those in the methylprednisolone group had a higher probability of achieving remission while receiving $\leq$5 mg oral prednisone at three time points: week 36 [RR 4.64 (CI 1.24, 17.33)], week 52 [RR 5.11 (CI 1.39–18.81)] and week 78 [RR 2.57 (CI 1.12, 5.89)] [90].

No differences were found between pulse therapy and control groups as regards discontinuation of glucocorticoids at 12 months (QoE +) [87], patients with at least one relapse at 78 weeks and drug-free remission at 78 weeks (both with QoE ++) [90].

Comparing adverse events between treatment arms in these trials, no differences were observed between the intervention and control groups regarding infections, cushingoid habitus, psychiatric side effects, cardiovascular complications, diabetes, digestive disturbances, glucocorticoid-related ophthalmologic side effects, phlebitis/thrombosis, glucocorticoid-induced myopathy, abdominal bleeding, osteoporosis including fractures and mortality (all with QoE + or ++). Nonetheless, the small size of these two trials limits the power to show significant differences in adverse events between treatment arms.

In summary, there may possibly be a small benefit in terms of a reduced cumulative glucocorticoid dose in patients receiving glucocorticoid intravenous pulse therapy, but due to concerns over the likely increased risk of adverse effects with this therapy, the value of intravenous glucocorticoids in patients without acute or intermittent visual loss in GCA remains uncertain.

3. Conditional recommendation: The standard initial glucocorticoid dose for GCA is 40–60 mg oral prednis(ol)one per day. QoE: +. Consensus score: 9.44.

What is the best dose and route of initial glucocorticoid therapy for GCA in the presence of ischaemic visual manifestations? (PICO 4). Clinical trials have not been conducted in patients with acute ocular ischaemia, but observational data indicate that the vast majority of visual loss in GCA occurs before initiation of glucocorticoid therapy. Acute visual loss due to ocular ischaemia in GCA requires immediate action [29].

Intravenous glucocorticoid (methylprednisolone) therapy is used in systemic vasculitis for the treatment of life- or organ-threatening disease [91]. The intravenous formulation ensures rapid delivery of the drug to the site of action and, in addition, the very high doses required have rapid actions via non-genomic effects as well as on the genomic effects that take some hours to affect gene transcription [92, 93]. Intravenous glucocorticoid therapy is thus commonly used for patients with acute or intermittent visual loss due to GCA. If intravenous glucocorticoid therapy is not possible, 60–100 mg oral prednisolone may be given for up to 3 consecutive days.

4. Conditional recommendation: GCA patients with acute or intermittent visual loss may initially be given 500 mg–1 g intravenous methylprednisolone daily for up to 3 consecutive days before commencing oral prednis(ol)one therapy. If intravenous therapy is not immediately possible, this should not delay initiation of oral prednis(ol)one. QoE: +. Consensus score: 9.00.

How should glucocorticoid dose be tapered in GCA? (PICO 5). A single-centre, open, 2-month RCT compared different tapering regimens in 35 patients with new-onset GCA [94]. The same glucocorticoid dose was used in the first 5 days, but the rate of tapering thereafter differed between treatment groups. No significant difference was found between the groups at 2 months

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concerning relapse rate (QoE +) or visual loss (QoE ++).

In a multicentre RCT of tocilizumab as a glucocorticoid-sparing therapy for GCA [52], in two arms of the trial patients received placebo rather than tocilizumab. In one of these trial arms prednisone was tapered to zero over 6 months and in the other prednisone was tapered to zero over 12 months; relapses were treated at the discretion of the investigator. Patients with new-onset GCA receiving the 6 month prednisone taper without tocilizumab had a numerically higher frequency of relapse during the first year than receiving the 12 month prednisone taper, whereas the cumulative glucocorticoid dose was similar in these two trial arms. Although patients and investigators were blinded to the tapering regimen, this trial was not designed specifically to compare different prednisone tapering regimens.

5. Conditional recommendation: Glucocorticoid dose should be tapered to zero over 12–18 months, providing there is no return of GCA symptoms, signs or laboratory markers of inflammation. A more rapid dose reduction is appropriate for patients at high risk of glucocorticoid toxicity and/or those receiving concomitant glucocorticoid-sparing therapy. QoE: +. Consensus score: 8.81.

What dosing frequency of oral glucocorticoid should be used in GCA? (PICO 6, 7). A single-centre, open RCT with unclear length of follow-up compared the effects of 15 mg oral prednisone every 8 h with a single administration of 45 mg oral prednisolone/day. A third (alternate day) group received 90 mg oral prednisone every other day. Patients in all three groups were treated for the first 5 days with 20 mg oral prednisone every 8 h [95].

Remission and relapses at 4 weeks did not differ between groups of split-dose and single-dose prednisone treatment (QoE +). No difference was reported regarding hypercortisolism (which was not further defined), fractures, diabetes and glucocorticoid-induced myopathy (all with QoE +).

Comparing the single-daily and alternate-day treatment groups, at 4 weeks the single-daily group had higher remission rates at 4 weeks [RR 2.67 (CI 1.32, 5.39)] and lower relapse rates [RR 0.11 (CI 0.02, 0.80)] (QoE +). Hypercortisolism was more common in the single-daily group [RR 5.95 (CI 1.57, 22.57)]; fractures, diabetes and glucocorticoid-induced myopathy (all with QoE +) did not differ between groups.

This evidence, albeit low quality, raises concerns that alternate-day dosing may be associated with a higher relapse risk. Splitting the dose over the day does not seem to confer benefit and potentially carries risks of disturbance of diurnal rhythms, including sleep [96, 97]. In summary, in GCA there appears to be no reason to alter the standard guidance in other medical conditions to prescribe glucocorticoids as a single daily dose in the morning [12, 91].

6. Conditional recommendation: Patients should be prescribed a single daily dose of glucocorticoid rather than alternate day dosing or divided daily dosing. QoE: +. Consensus score: 9.53.

Should modified-release prednisone be used in place of standard therapy? (PICO 8). There was neither RCT data nor sufficient clinical experience to make any recommendation about modified-release prednisone in GCA.

7. No recommendation can be made for the use of modified-release prednisone in the treatment of GCA. QoE: insufficient evidence. Consensus score: 9.72.

When should further, non-biologic immunosuppression be added to glucocorticoid therapy for GCA? (PICO 9, 10). The effect of MTX has been investigated in three RCTs: a single-centre, 24-month, double-blinded RCT ($n = 42$) of patients with recent-onset GCA compared the addition of MTX 10 mg/week, *vs* placebo, to oral prednisone (initial prednisone dose of 60 mg/day) [98]. A multicentre, 12-month, double-blinded RCT ($n = 98$ instead of 300 originally planned) of patients with recent-onset GCA compared the addition of MTX 15 mg/week, *vs* placebo, to oral prednisone (initial prednisone dose of 1 mg/kg/day) [88]. A smaller single-centre, double-blinded RCT ($n = 21$) of patients with GCA whose prednisone dose had been reduced to 30 mg/day compared the adjunctive use of MTX 7.5 mg/week *vs* placebo; the initial glucocorticoid dose was at the discretion of the treating physician and some patients with visual symptoms received intravenous glucocorticoid pulse therapy [99].

Regarding efficacy data, the two larger trials [88, 98] could be pooled but the smallest trial [99] was considered separately because it substantially differed from the two other trials regarding design (lower MTX dose used, initiation of therapy upon reduction of glucocorticoid dose) and quality. Regarding adverse events, we combined the data from all three trials in order to increase the sensitivity to detect rare outcomes.

Pooling of the two larger studies indicated moderate QoE (+++) that MTX reduced the proportion with relapse at 12–24 months [RR 3.20 (95% CI 1.49, 6.87)] [88, 98]; the smallest trial showed no difference in relapse between the MTX and placebo groups (QoE +) [99]. In addition, the largest trial analysed 'treatment failure', defined as having two or more relapses or having a relapse that was not controlled by an increment of prednisone dose as scheduled: regarding this outcome, no difference was seen between the MTX and placebo groups (QoE ++) [88]. In none of the studies was a difference observed regarding cumulative glucocorticoid dose or the duration of glucocorticoid therapy (all outcomes with QoE + or ++); however, the largest trial reported only the median and IQR of the cumulative glucocorticoid dose rather than the mean and standard deviation, which reduced the validity of pooling the published data [88, 98, 99].

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Regarding possible modification of glucocorticoid-related adverse effects by MTX, mortality, vision loss, malignancy, infections, psychiatric side effects, fractures, cataracts, diabetes, hypertension, cushingoid habitus, weight gain and skin fragility did not differ between groups (data from one to three studies, all with QoE + or ++, except for hypertension, with QoE +++) [88, 98, 99].

Regarding possible MTX-related adverse effects, there was no strong evidence to support that MTX was associated either with a higher rate of withdrawal due to any side effect, nor an increase in individual side effects, including alanine aminotransferase/aspartate transaminase elevation, nausea/vomiting, thrombocytopenia, oral ulcers, alopecia, diarrhoea or gastric discomfort (QoE + or ++) [88, 98, 99]. Nonetheless, these trials were not designed nor powered to detect differences in adverse effects.

An individual patient data meta-analysis relating to these three RCTs was also identified [100] and included in this review because it is a more efficient use of the data than meta-analysis using published reports. According to the individual patient data meta-analysis, compared with the placebo group, the MTX group had a modest reduction of the risk of first and second relapse (HR 0.65, $P = 0.04$ and HR 0.49, $P = 0.02$, respectively), higher rates of glucocorticoid-free remission (HR 2.8, $P = 0.001$ for ≥24 weeks sustained discontinuation of glucocorticoids) and lower cumulative glucocorticoid doses (mean difference −1.1 g, $P = 0.007$ at week 96) [100].

In summary, the data from these three small RCTs indicate that there might be a modest benefit of MTX in GCA in reducing relapse and cumulative glucocorticoid dose and the data are encouraging regarding reducing the risk of second relapse as well as first relapse; however, overall the evidence remains equivocal. MTX has been used at doses of 7.5–15 mg weekly in clinical studies and up to 25 mg weekly orally or by subcutaneous injection in clinical practice.

A single-centre, 52-week, double-blinded RCT ($n = 31$) compared azathioprine 150 mg/day *vs* placebo in patients with PMR, with or without GCA, who required ≥5 mg daily oral prednisolone to control disease activity [101]. A lower daily glucocorticoid dose at the end of the follow-up (52 weeks) was found in the intervention group compared with the control group [mean dose difference 3 mg (CI 4.32, 0.28), QoE +]. Adverse events were similar in both groups (QoE +). Thirty-one patients were recruited, but only 18 reached the 52 week time point. According to the inclusion criteria for this trial, patients had to satisfy the Hazleman criteria for PMR. Eleven of 31 of these had a positive temporal artery biopsy. This trial did not truly fulfil the inclusion criteria for this review (at least 20 patients with GCA) and therefore no recommendation could be made on the basis of this trial. However, it is included here for completeness since it is frequently mentioned by narrative reviews.

Dapsone was studied at a dose of 50–100 mg/day in an open, multicentre RCT ($n = 47$) with an unclear length of follow-up [102]. A lower relapse risk was found in the treatment group compared with the control group [RR 0.37 (CI 0.16, 0.84), QoE +] and there was a trend towards a higher probability of glucocorticoid-free remission [RR 3.81 (CI 0.92, 15.81), QoE +] in the dapsone group. Anaemia was more common in the dapsone group compared with the control group [RR 8.89 (CI 1.27, 61.99), QoE ++] and the dapsone group had two cases of agranulocytosis. Rash, diabetes, bone complications, cardiovascular complications, infections and loss of vision did not differ between groups (all QoE +).

Two open RCTs of ciclosporin ($n = 82$) were published in the format of a letter [103, 104]. Ciclosporin was used at a daily dose of 2.0–3.5 mg/kg for 6 or 12 months. No benefit of the drug was observed regarding cumulative glucocorticoid dose, acute phase reactants or patients' and physicians' global assessments (all QoE +). However, there was an increased risk of treatment discontinuation due to toxicity [RR 13.00 (CI 1.78, 95.1), QoE ++].

The potential toxicity of dapsone or ciclosporin is likely to outweigh any possible benefit and their use is not recommended. There has been no RCT of leflunomide in GCA despite anecdotal evidence of benefit in case series and open, non-randomized studies [105–107]. In clinical practice, mycophenolate mofetil or cyclophosphamide have been occasionally used as immunosuppressive agents for severe GCA by analogy with their use in other systemic vasculitides, but they have not been formally studied in GCA.

8. Conditional recommendation: MTX might be considered for GCA, in combination with a glucocorticoid taper, in patients at high risk of glucocorticoid toxicity or who relapse. There is insufficient evidence to recommend any other oral immunosuppressive agent in GCA, including azathioprine, leflunomide or mycophenolate mofetil. QoE: ++. Consensus score: 8.92.

Which biologic agents can be used for GCA in addition to standard therapy? (PICO 11, 12). Tocilizumab was approved for GCA by US and European regulatory authorities in 2017 based on the results of two RCTs of addition of 1 year tocilizumab, or placebo, to tapering glucocorticoid therapy [52, 89].

In the larger of these trials [52], both patients with new GCA and patients with relapsing GCA were included. Patients with relapsing GCA had to have been treated for GCA no longer than 4 years prior to enrolment. Tocilizumab was combined with a standardized prednisone taper according to which prednisone cessation occurred at 6 months. Patients receiving placebo were treated with one of two alternative prednisone tapering schedules, by which prednisone cessation was achieved at either 6 months or 1 year if the patient remained relapse-free. If a patient relapsed during the study, prednisone therapy was escalated according to the investigator's discretion.

The primary endpoint (sustained remission at 1 year plus adherence to the tapering protocol, using a definition of remission incorporating CRP levels) was

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achieved in 56% of patients treated with weekly subcutaneous tocilizumab and in 53% of those treated every other week. In the placebo group, sustained remission at 1 year was achieved in 14% of those tapering prednisone over 6 months and 18% of those tapering prednisone over 1 year. Comparing weekly tocilizumab with placebo plus a 6 month glucocorticoid taper, the RR for sustained remission was 4.0 (95% CI 1.97, 8.12; QoE++++). Comparisons with other groups revealed similar results, with an RR of 3.01–3.79 (QoE ++++). Patients in the tocilizumab treatment arm also showed a higher rate of sustained remission using a modified definition of sustained remission that did not require CRP normalization [weekly tocilizumab compared with placebo plus a 6 month glucocorticoid taper: RR 2.95 (95% CI 1.66, 5.26), QoE +++; for other comparisons, RR 1.65–2.76, QoE+++].

In both this trial and in the smaller single-centre trial [89], an increase in relapse-free survival at 1 year [RR 3.57 (95% CI 2.29, 5.55), QoE ++++] was seen and a reduction in the 1 year cumulative glucocorticoid dose was observed in the tocilizumab treatment arms [mean difference −1434 mg (95% CI −2148, −720) in the weekly tocilizumab group compared with placebo plus 6 month tapering of glucocorticoids, QoE++++; mean difference from −1434 to −1956 mg in other comparisons, QoE++++]. Patient-reported outcomes were encouraging, although these were assessed using generic measures, since no disease-specific patient-reported outcome has yet been fully validated for GCA. Of note, although glucocorticoid-sparing efficacy was demonstrated, these studies were not designed or powered to demonstrate a reduction in glucocorticoid-related adverse events.

It has been argued that a glucocorticoid-sparing therapy such as tocilizumab would be more cost effective in the following GCA patient subgroups: first, GCA patients requiring escalation of glucocorticoid therapy due to relapse of disease, and second, GCA patients who are at high risk for adverse effects from further glucocorticoid treatment (e.g. on the basis of their comorbidity profile or other risk factors for glucocorticoid-related toxicity, including neuropsychiatric glucocorticoid-related adverse effects, previous fragility fractures or difficult-to-control diabetes mellitus).

UK prescribers should be aware that, at the time of writing, a limited duration of tocilizumab therapy for GCA has been approved by the Scottish Medicines Consortium and by NHS England for defined patient groups, taking into account cost-effectiveness data available at the time of the technology appraisal.

Tocilizumab has only been approved for weekly subcutaneous use, although it has also been studied in intravenous formulations [89]. In a multicentre RCT [52], one of the treatment arms received subcutaneous tocilizumab every 2 weeks rather than weekly; patients in this treatment arm also reached the primary endpoint, although it appeared to be less efficacious in relapsing patients. The trials in GCA have not demonstrated an increased risk of adverse events with tocilizumab [52, 89]; pooling of data from both trials indicated a lower rate of serious adverse events in patients treated with tocilizumab than those treated with placebo [RR 0.64 (95% CI 0.41, 1.00), QoE+++].

Abatacept was studied in a single, small trial [108]. All patients received abatacept initially in addition to glucocorticoid therapy. Those achieving remission were randomized in week 12 to either continue the drug or to switch to placebo. Time-to-relapse analysis, which was the primary endpoint, significantly favoured abatacept. A post hoc analysis to compare the proportion of patients in remission at 12 months did not show a significant difference between the treatment arms [RR 1.50 (CI 0.71, 3.17), QoE ++], likely due to the small size of the study. At present, abatacept is not approved for treatment of GCA.

TNF inhibitors have been studied in two RCTs [109, 110], both of which showed inefficacy but an increased incidence of infections. A third, small RCT of etanercept for GCA [111] did not fulfil the inclusion criteria for the literature review. Although it showed a lower cumulative glucocorticoid dose in the etanercept arm, this trial failed to show a significant result for its primary outcome. Based on this evidence, TNF inhibitors cannot be recommended for GCA.

9. Strong recommendation: Tocilizumab can be considered for GCA, in combination with a glucocorticoid taper, especially in patients at high risk of glucocorticoid toxicity or who relapse. TNF inhibitors are not recommended in GCA. QoE: +++. Consensus score: 9.61.

Should anticoagulant or antiplatelet agents be given for GCA? (PICO 12–15). No RCTs relating to aspirin or other anticoagulant/antiplatelet agents were found. A Cochrane review found no evidence from RCTs to determine the safety and efficacy of low-dose aspirin as an adjunctive treatment in GCA [112]. National and society guidelines for the secondary prevention of coronary and other atherosclerotic vascular diseases should be followed.

10. The routine use of antiplatelet or anticoagulant agents for GCA is not recommended. QoE: insufficient evidence. Consensus score: 9.28.

Should cholesterol-lowering agents be given for GCA? (PICO 16). No RCTs of cholesterol-lowering agents for GCA were found. National and society guidelines for the secondary prevention of coronary and other atherosclerotic vascular diseases should be followed.

11. The routine use of cholesterol-lowering agents such as statins for GCA is not recommended. QoE: insufficient evidence. Consensus score: 9.53.

Applicability and utility

This guideline represents a framework upon which clinical practice should be based. However, as with any guideline, individual patient circumstances can have important influences on clinical decision making and clinicians should continue to work alongside patients to make shared decisions about care. Failure to adhere to this guideline should not necessarily be considered

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negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence.

Potential organizational barriers to implementation

In practice, constraints of the healthcare system may create challenges to widespread implementation of this guideline. For example, implementing rapid-access vascular ultrasound as a diagnostic test in GCA is dependent not only on local expertise and experience in the technique itself, but also on the entire care pathway for patients with suspected GCA, including appropriate, timely referrals and clinical expertise such that the results of the test can be interpreted appropriately.

As another example, follow-up every 2–8 weeks for the first 6 months (less frequently thereafter) may seem ambitious, but this could be delivered via a shared care model in collaboration with primary care by which the patient and general practitioner receive the information and support they need and have ready access to secondary care if need be. Nonetheless, it is also recognized that specific quality standards are necessary to drive clinical improvement.

Cost and cost-effectiveness implications for implementation

A formal health economic evaluation was not conducted as part of the guideline development process.

The use of additional imaging tests could incur healthcare costs. This has to be set against the advantages of accurate, timely diagnosis of GCA, in particular the potential cost savings of avoiding unnecessary treatment of patients without the disease.

A UK National Institute for Health and Care Excellence (NICE) technology appraisal has been conducted with regard to tocilizumab therapy for GCA [113], which has the potential to significantly increase the direct costs of drug treatment of GCA. Both biologic and non-biologic therapies used alongside glucocorticoid treatment would incur additional costs due to the requirements for regular blood monitoring. However, this must be set against the potential cost savings arising from a reduction in cumulative glucocorticoid doses and thereby a reduction in glucocorticoid-associated adverse events. On the basis of overall cost-effectiveness data, approval was granted by NHS England and the Scottish Medicines Consortium for tocilizumab treatment for defined GCA patient groups; readers are directed to the appropriate guidance for a more detailed explanation.

Mechanism for auditing compliance with the guideline

Quality standards have been defined based on the fundamentals of good clinical care, as outlined in the general principles. Audit should be performed on an unbiased (e.g. consecutive) sample of patients presenting to a clinic or service. A draft audit tool that may be adapted for local use is published as Fig.

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Statement of contribution of the literature review team

Christian Dejaco led the SLR team. The literature review team was split into three groups, each group consisting of three members: group 1 (Duftner, Mackie, Appenzeller) performed the SLR on diagnostic tests/strategies, group 2 (Dejaco, Camellino, Hutchings) performed the SLR on therapeutic interventions and group 3 (Mahr, Gonzalez-Chiappe, Wagner Silva de Souza) performed the SLR on prognostic factors. Two members of each group independently performed screening, inclusion/exclusion of articles, data extraction and quality appraisal. Results were compared between the two members and any discordance was resolved by discussion, then consulting the third member of the group where no consensus could be reached. Christian Dejaco supervised the progress of the SLR in each group and the preparation of the evidence tables. The searches underpinning the 2018 update to the SLR were conducted by Gary Reynolds, who also worked with the literature review team in the appraisal of new evidence.

Individuals who contributed to the guideline development but did not participate in the final voting are listed below and their contributions are gratefully acknowledged:

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Presentation and dissemination of final guidelines

The final guidelines will be disseminated by publication in the journal Rheumatology (Oxford) as well as by uploading onto the BSR homepage.

Funding: The British Society for Rheumatology provided financial support for this guideline.

Disclosure statement: Christian Dejaco – received consultancy fees and honoraries from Roche, Sanofi, AbbVie, MSD, Pfizer, UCB, Bristol-Myers Squibb; first author of EULAR imaging recommendations in large vessel vasculitis, first author of ACR/EULAR recommendations for management of PMR, co-author of management recommendations for large vessel vasculitis.

Simone Appenzeller – none.

Dario Camellino – received travel expenses, consultancy fees and speaker fees from AbbVie, Celgene, Janssen-Cilag, Eli Lilly, Mylan and Sanofi.

Christina Duftner – none.

Solange Gonzalez-Chiappe – none.

Alfred Mahr – received honoraria for advisory board meetings and lectures from Chugai Pharma France.

Chetan Mukhtyar – none.

Gary Reynolds – none.

Alexandre Wagner Silva de Souza – none.

Elisabeth Brouwer – an employee of the University Medical Center Groningen, Groningen, The Netherlands. Part of the work is funded by Reuma Nederland, lead author in the development of local and national guidelines for GCA in The Netherlands.

Marwan Bukhari – involved in the GCA Consortium, which is indirectly funded by Roche/Chugai, and virtual advisory board member for Roche/Chugai on GCA.

Frank Buttgereit – received consultancy fees, honoraria and/or travel expenses from Horizon Pharma, Mundipharma, Roche and Pfizer and grant/study support from Horizon Pharma and Mundipharma.

Dorothy Byrne – vice chair of PMRGCAuk.

Maria C. Cid – received a research grant from Kiniksa and consulting fees from AbbVie and Janssen, participated in clinical trials sponsored by GlaxoSmithKline and Kiniksa and co-author in publications of work sponsored by Roche.

Marco Cimmino – none.

Haner Direskeneli – local advisory board member for Roche for GCA.

Kate Gilbert – representative of PMRGCAuk.

Tanaz A. Kermani – received consultancy fees from AbbVie in March 2018.

Asad Khan – received speaker fees from Chugai.

Peter Lanyon – former president of the BSR (April 2016–18) and chair of the Rare Autoimmune Rheumatic Disease Alliance (RAIRDA).

Raashid Luqmani – received grants, honoraria and travel support for EULAR 2019 from Roche/Chugai.

Christian Mallen – none.

Justin C. Mason – received speaker fees and consultancy fees from Roche/Chugai.

Eric L. Matteson – none.

Peter A. Merkel – received consulting fees from AbbVie, AstraZeneca, Biogen, Boeringher-Ingelheim, Bristol-Myers Squibb, Celgene, ChemoCentryx, CSL Behring, Genentech/Roche, Genzyme/Sanofi,

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GlaxoSmithKline, InflaRx, Insmed, Janssen and Kiniksa and research support from Bristol-Myers Squibb and Genentech/Roche/Chugai.

Susan Mollan – advisory board member and received speaker fees from Roche/Chugai, representative of the Royal College of Ophthalmologists, co-author of the EULAR GCA guideline group and co-author of the European Headache Federation GCA guideline group.

Lorna Neil – chair of PMR-GCA Scotland and patient representative for the EULAR working group on imaging in LVV.

Eoin O'Sullivan – none.

Maria Sandovici – none.

Wolfgang A. Schmidt – received consulting fees from GlaxoSmithKline, Novartis, Roche and Sanofi; member of the speaker's bureau for Chugai, GlaxoSmithKline, Novartis, Roche and Sanofi and participated in trials/studies for GlaxoSmithKline, Novartis, Roche and Sanofi.

Richard Watts – none.

Madeline Whitlock – none.

Elaine Yacyshyn – none.

Steven Ytterberg – none.

Bhaskar Dasgupta – received consultancy fees for membership on clinical trials advisory boards and for developing trial protocols; speaker fees from Roche-Chugai, Sanofi, ERT, Bristol-Myers Squibb, GlaxoSmithKline and AbbVie and ultrasound workshop/GCA symposium grants to Southend University Hospital; honorary president of PMRGCAuk; television appearance on BBC2 health program 'Trust me, I'm a doctor', released February 2017.

Sarah Mackie – patron of PMRGCAuk, founding member of the TARGET Research Consortium, co-chair of the OMERACT PMR Working Group, member of the OMERACT Vasculitis Working Group, subinvestigator for the licensing RCT of tocilizumab for giant cell arteritis (GiACTA; site principal investigator) and for sirukumab for giant cell arteritis (SIRRESTA; local principal investigator) and UK clinical investigator for an international multicentre industry-sponsored trial of sarilumab for GCA and attendance at EULAR 2019 supported by Roche/Chugai.

Disclaimer: The views expressed are those of the authors and not necessarily those of the National Institute for Health Research or the UK Department of Health and Social Care.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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RHEUMATOLOGY

Guidelines

Rheumatology 2010;49:186–190
doi:10.1093/rheumatology/kep303a
Advance Access publication 12 November 2009

BSR and BHPR guidelines for the management of polymyalgia rheumatica

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Key words: Guidelines, Polymyalgia rheumatica, Diagnosis, Treatment, Corticosteroid.

Executive summary

Scope and purpose

PMR is the most common inflammatory rheumatic disease in the elderly and is one of the biggest indications for long-term steroid therapy. There are difficulties in diagnosis, with heterogeneity in presentation, response to steroids and disease course.

The aim of these guidelines is a safe and specific diagnostic process for PMR, using continued assessment, and discouragement of hasty initial treatment. Their scope is to provide advice for the diagnosis of PMR, management and monitoring of disease activity, complications and relapse. The management of GCA is not covered and is published separately.

The full guideline is available at *Rheumatology* online.

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Submitted 26 May 2009; revised version accepted 13 August 2009.

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Guidelines

(1) We recommend that a safe, stepped diagnostic process be adopted for the evaluation of PMR (Strength of recommendation C).

Diagnosis of PMR should start with evaluation of core inclusion and exclusion criteria, followed by assessment of the response to a standardized dose of steroid [1]. Atypical features or response to steroid should prompt consideration of alternative pathology, and specialist referral.

Unlike with GCA, urgent institution of steroid therapy is not necessary and can be delayed to allow full assessment. However, if the patient does present with symptoms suspicious of GCA, then urgent institution of high-dose steroid therapy is needed (see Guidelines for Management of GCA).

(i) Core inclusion criteria:

- Age >50 years, duration >2 weeks
- Bilateral shoulder or pelvic girdle aching, or both
- Morning stiffness duration of >45 min
- Evidence of an acute-phase response

PMR can be diagnosed with normal inflammatory markers, if there is a classic clinical picture and response to steroids. These patients should be referred for specialist assessment.

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(ii) Core exclusion criteria:

- Active infection
- Active cancer
- Active GCA (see part iii)

The presence of the following conditions decreases the probability of PMR, and they should also be excluded:

- Other inflammatory rheumatic diseases
- Drug-induced myalgia
- Chronic pain syndromes
- Endocrine disease
- Neurological conditions, e.g. Parkinsons disease

(iii) Patients should be assessed for evidence of GCA, as this requires urgent institution of high-dose steroid (see separate guidelines)

- Abrupt-onset headache (usually temporal) and temporal tenderness
- Visual disturbance, including diplopia
- Jaw or tongue claudication
- Prominence, beading or diminished pulse on examination of the temporal artery
- Upper cranial nerve palsies
- Limb claudication or other evidence of large-vessel involvement

(iv) Patients should be assessed for response to an initial standardized dose of prednisolone 15 mg daily orally [1, 2].

A patient-reported global improvement of $\geqslant$70% within a week of commencing steroids is consistent with PMR, with normalization of inflammatory markers in 4 weeks. A lesser response should prompt the search for an alternative condition.

(v) The diagnosis of PMR should be confirmed on further follow-up [2]. Follow-up visits should include vigilance for mimicking conditions.

(2) We recommend documentation in the patient's medical record of a minimum data set, which forms the basis for the diagnosis.

- The core clinical inclusion and any exclusion criteria
- Laboratory investigations before commencement of steroid therapy
  - Full blood count
  - ESR/plasma viscosity and/or CRP
  - Urea and electrolytes
  - Liver function tests
  - Bone profile
  - Protein electrophoresis (also consider urinary Bence Jones Protein)
  - Thyroid stimulating hormone
  - Creatine kinase
  - RF (ANA and anti-CCP antibodies may be considered)
  - Dipstick urinalysis
  - Chest X-ray may be required

(3) We recommend the following approach for the evaluation of proximal pain and stiffness [3] (Fig. 1).

(4) We recommend early specialist referral in the following circumstances (C).

Atypical features or features that increase likelihood of a non-PMR diagnosis:

- Age <60 years
- Chronic onset (>2 months)
- Lack of shoulder involvement
- Lack of inflammatory stiffness
- Prominent systemic features, weight loss, night pain, neurological signs
- Features of other rheumatic disease
- Normal or extremely high acute-phase response

Treatment dilemmas such as:

- Incomplete, poorly sustained or non-response to corticosteroids
- Inability to reduce corticosteroids
- Contraindications to corticosteroid therapy
- The need for prolonged corticosteroid therapy (>2 years)

However, patients with a typical clinical picture and complete sustained response to treatment, and no adverse events can be managed in primary care.

(5) We recommend initiation of low-dose steroid therapy with gradually tailored tapering in straightforward PMR (B).

In the absence of GCA, urgent steroid therapy is not indicated before the clinical evaluation is complete.

The suggested regimen is:

- Daily prednisolone 15 mg for 3 weeks
- Then 12.5 mg for 3 weeks
- Then 10 mg for 4–6 weeks
- Then reduction by 1 mg every 4–8 weeks or alternate day reductions (e.g. 10/7.5 mg alternate days, etc.)

However, there is no consistent evidence for an ideal steroid regimen suitable for all patients. Therefore, the approach to treatment must be flexible and tailored to the individual as there is heterogeneity in disease course. Some benefit from a more gradual steroid taper. Dose adjustment may be required for disease severity, comorbidity, side effects and patient wishes.

Intramuscular methylprednisolone (i.m. depomedrone) may be used in milder cases and may reduce the risk of steroid-related complications. Initial dose is 120 mg every 3–4 weeks, reducing by 20 mg every 2–3 months [4].

Usually 1–2 years of treatment is needed [5]. The need for ongoing therapy after 2 years of treatment should prompt the consideration of an alternative diagnosis, and referral for specialist evaluation.

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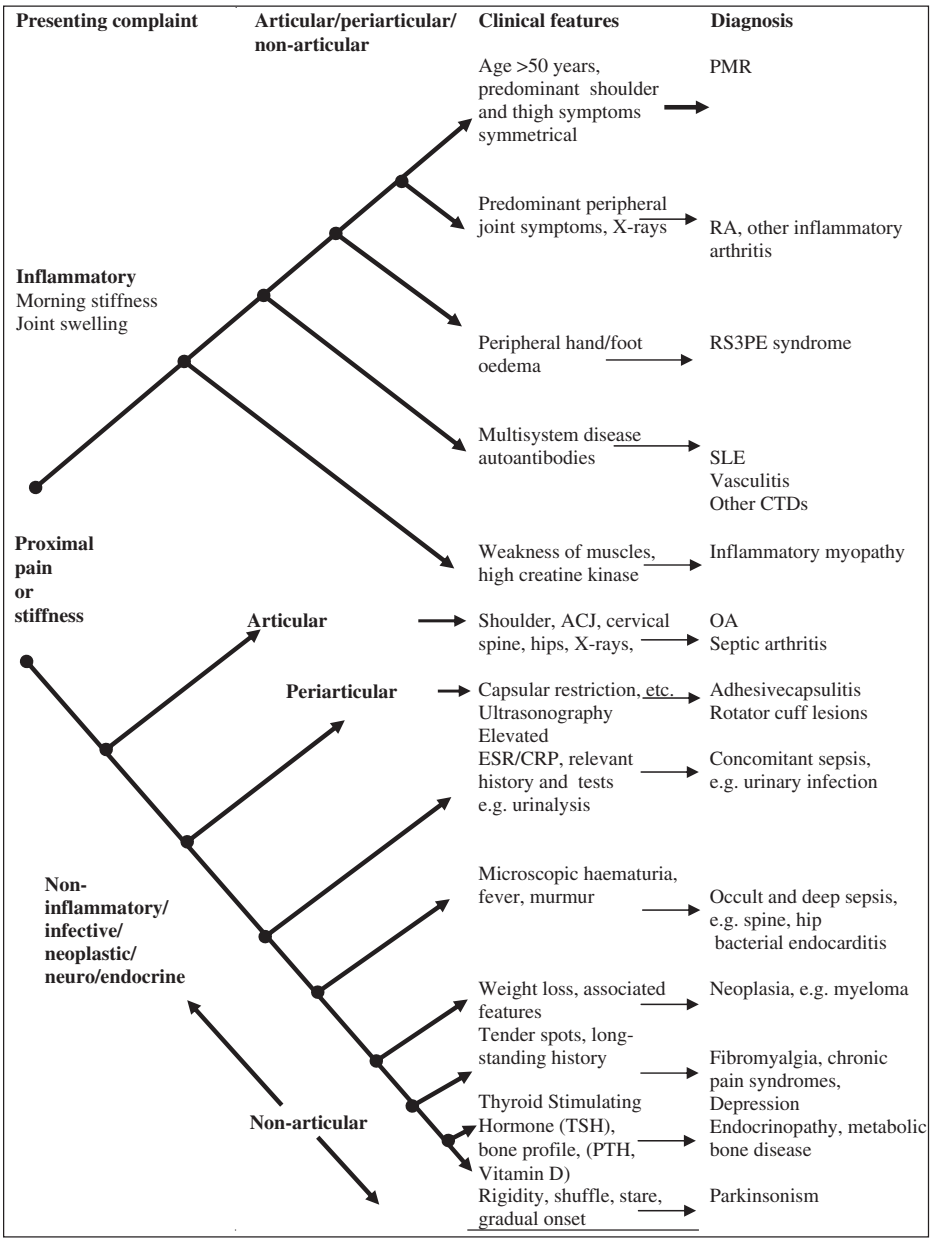
FIG. 1 Approach to the evaluation of proximal pain and stiffness. ACJ: acromio-clavicular joint.



(6) We recommend the use of bone protection when initiating steroids for PMR to prevent the complications of osteoporosis (A−).

- Individuals with high fracture risk, e.g. aged ⩾65 years or prior fragility fracture
  - Bisphosphonate with calcium and vitamin D supplementation
  - DEXA not required
- Other individuals
  - Calcium and vitamin D supplementation when starting steroid therapy.
  - DEXA scan recommended
  - A bone-sparing agent may be indicated if *T*-score is −1.5 or lower.
- Individuals requiring higher initial steroid dose
  - Bisphosphonate with calcium and vitamin D supplementation (because higher cumulative steroid dose is likely)

(7) We recommend vigilant monitoring of patients for response to treatment and disease activity (B).

Follow-up schedule:

Weeks 0, 1–3, 6, Months 3, 6, 9, 12 in first year (with extra visits for relapses or adverse events).

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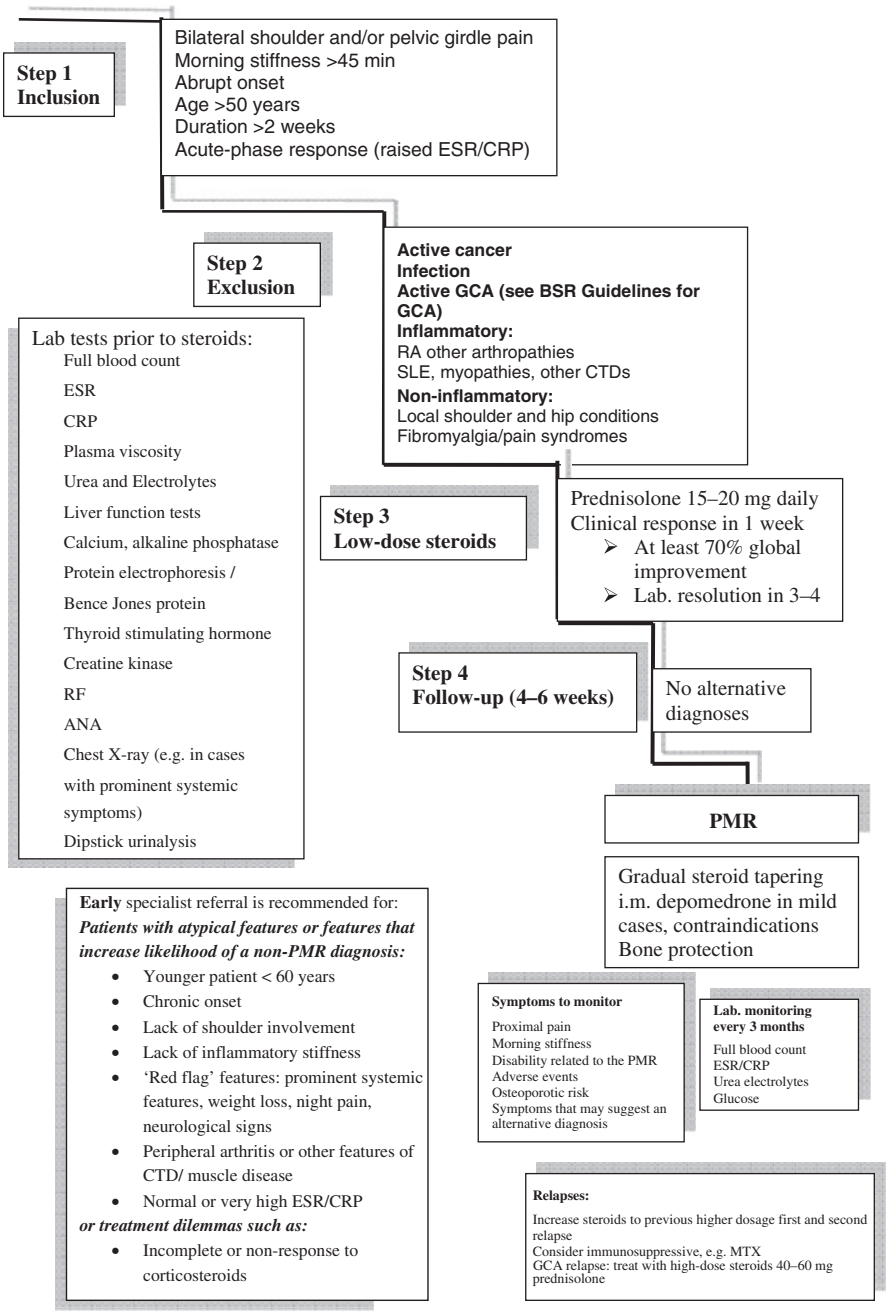
FIG. 2 Approach to diagnosis and management of polymyalgia.



Early follow-up is necessary as part of the diagnosis to evaluate response to initial therapy [2], and the first follow-up should occur at 1–3 weeks before commencement of steroids.

Clinical assessment:

At each visit, patients should be assessed for the following:

- Response to treatment: proximal pain, fatigue and morning stiffness

It is important to distinguish between symptoms due to inflammation and those due to co-existing degenerative problems.

- Complications of disease including symptoms of GCA, e.g. headaches, jaw claudication and large-vessel disease
- Steroid-related adverse events
- Atypical features or those suggesting an alternative diagnosis

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Laboratory monitoring:

- Full blood count, ESR/CRP, urea and electrolytes, glucose

Duration of treatment and follow-up:

- Usually 1–3 years of treatment, although some will require small doses of steroids beyond this. Flexibility in approach is necessary given the heterogeneous nature of disease. Steroids may be stopped when the patient is asymptomatic from their inflammatory symptoms.
- Isolated raised ESR or CRP is not an indication for continuing steroid therapy but may require investigation and referral.
- Persistent pain may arise from co-existing OA and rotator cuff tears.

(8) We recommend the following approach to relapse of disease.

Relapse is the recurrence of symptoms of PMR or onset of GCA, and not just unexplained raised ESR or CRP [6].

Treatment of relapse:

- Clinical features of GCA: treat as GCA (usually oral prednisolone 40–60 mg daily) (see GCA guideline)
- Clinical features of PMR: increase prednisolone to previous higher dose.
- Single i.m. injection of methylprednisolone (depomedrone) 120 mg can also be used.
- Further relapses: consider introducing DMARD therapy after two relapses

The approach to diagnosis and management of PMR is summarized in Fig. 2.

Patient education

An ARC patient information booklet is available. Further support is available from local patient groups under the auspices of PMRGCA-UK.

Recommendations for audit

Audit standards should include the minimum data set recorded prior to steroid therapy, initial steroid dose and taper, monitoring schedule, use of bone protection and provision of patient information.

Outcomes measures include disease relapse, persistent disease activity, cumulative steroid dosage, adverse events and complications of therapy and quality of life.

Disclosure statement: The authors have declared no conflicts of interest.

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Arthritis Care & Research
Vol. 73, No. 8, August 2021, pp 1071–1087
DOI 10.1002/acr.24632
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2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions, and drug formularies or other third-party analyses that cite ACR guidelines should state this. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

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Objective. To provide evidence-based recommendations and expert guidance for the management of giant cell arteritis (GCA) and Takayasu arteritis (TAK) as exemplars of large vessel vasculitis.

Methods. Clinical questions regarding diagnostic testing, treatment, and management were developed in the population, intervention, comparator, and outcome (PICO) format for GCA and TAK (27 for GCA, 27 for TAK). Systematic literature reviews were conducted for each PICO question. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to rate the quality of the evidence. Recommendations were developed by the Voting Panel, comprising adult and pediatric rheumatologists and patients. Each recommendation required ≥70% consensus among the Voting Panel.

Results. We present 22 recommendations and 2 ungraded position statements for GCA, and 20 recommendations and 1 ungraded position statement for TAK. These recommendations and statements address clinical questions relating to the use of diagnostic testing, including imaging, treatments, and surgical interventions in GCA and TAK. Recommendations for GCA include support for the use of glucocorticoid-sparing immunosuppressive agents and the use of imaging to identify large vessel involvement. Recommendations for TAK include the use of nonglucocorticoid immunosuppressive agents with glucocorticoids as initial therapy. There were only 2 strong recommendations; the remaining recommendations were conditional due to the low quality of evidence available for most PICO questions.

Conclusion. These recommendations provide guidance regarding the evaluation and management of patients with GCA and TAK, including diagnostic strategies, use of pharmacologic agents, and surgical interventions.

INTRODUCTION

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are systemic vasculitides that primarily affect large- and medium-sized vessels (1). GCA can present with both cranial and extracranial manifestations. Cranial manifestations include headaches, scalp tenderness, vision loss, and jaw claudication. Large vessel ("extracranial") involvement results in arterial stenosis and aneurysms, causing absent pulses and limb claudication (2). GCA is more common in individuals of Northern European descent who are older than 50 years of age. Diagnosis is based on clinical presentation, pathologic abnormalities on temporal artery biopsy, and/or evidence of large vessel involvement on vascular imaging (1–6). Glucocorticoids are the mainstay treatment for GCA, but tocilizumab has been approved by the US Food and Drug Administration for the treatment of GCA (7,8).

TAK causes granulomatous inflammation of the aorta and its branches. It is more common in younger women (9,10). Clinical manifestations include constitutional symptoms, elevated levels of inflammation markers, and arterial stenosis and/or aneurysms resulting in limb claudication and absent pulses (11). Treatment options include glucocorticoids, nonglucocorticoid immunosuppressive agents, and surgical management of vascular abnormalities (12).

As GCA and TAK share clinical manifestations, similar questions arise regarding their treatment and management. Recent studies have broadened treatment options for GCA, and vascular imaging is increasingly used for diagnosis and management. This guideline was developed to provide evidence-based recommendations for the evaluation and management of GCA and TAK.

METHODS

This guideline followed the American College of Rheumatology (ACR) guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and develop recommendations (13–15). ACR policy guided the management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis). Supplementary Appendix 1 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract) presents a detailed description of the methods. Briefly, the Literature Review team undertook systematic literature reviews for predetermined questions specifying the clinical population, intervention, comparator, and outcomes (PICO). An in-person Patient Panel of 11 individuals with different types of vasculitis (3 patients with GCA or TAK) was moderated by a member of the Literature Review team (ABD). This Patient Panel reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives and preferences about their personal experiences regarding clinical and treatment aspects of their disease. The Voting Panel comprised 9 adult rheumatologists, 5 pediatric rheumatologists, and 2 patients; they reviewed the Literature Review team's evidence summaries and, bearing in mind the Patient Panel's deliberations, formulated and voted on recommendations. A recommendation required ≥70% consensus among the Voting Panel.

The article is published simultaneously in *Arthritis & Rheumatology*.

Supported by the American College of Rheumatology and the Vasculitis Foundation.

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Dr. Langford has received consulting fees, speaking fees, and/or honoraria from Bristol Myers Squibb (less than $10,000) and research grants from Bristol Myers Squibb, GlaxoSmithKline, and Genentech. Dr. Grayson has submitted a patent application for the diagnosis and treatment of vacuoles, E1 enzyme, x-linked, autoinflammatory, somatic (VEXAS) syndrome. Dr. Merkel has received consulting fees, speaking fees, and/or honoraria from AbbVie, Biogen, Bristol Myers Squibb, CSL Behring, Genentech/Roche, Genzyme/GlaxoSmithKline, Insmed, Janssen, Kiniksa, Kyverna, Pfizer, Sparrow, and Takeda (less than $10,000 each) and from AstraZeneca, InflaRx, and ChemoCentryx (more than $10,000 each), research support from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, ChemoCentryx, Forbius, Genentech/Roche, Sanofi-Genzyme, GlaxoSmithKline, and InflaRx, and royalties from *UpToDate*. Dr. Stone has received consulting fees, speaking fees, and/or honoraria from Roche and Genentech (less than $10,000 each). Dr. Sule holds a patent related to the development of the Glucocorticoid Toxicity Index. Dr. Sundel has received royalties from *UpToDate*. Dr. Dua has received consulting fees, speaking fees, and/or honoraria from ChemoCentryx and AbbVie (less than $10,000 each). No other disclosures relevant to this article were reported.

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Submitted for publication September 25, 2020; accepted in revised form April 13, 2021.

How to interpret the recommendations

A *strong* recommendation is typically supported by moderate- to high-quality evidence (e.g., multiple randomized controlled trials). For a strong recommendation, the recommended course of action would apply to all or almost all patients. Only a small proportion of clinicians/patients would not want to follow the recommendation. In rare instances, a strong recommendation may be based on very low– to low-certainty evidence. For example, an intervention may be strongly recommended if it is considered low-cost, without harms, and the consequence of not performing the intervention may be catastrophic. An intervention may be strongly recommended against if there is high certainty that the intervention will lead to more harm than the comparison with very low or low certainty about its benefit (16).

A *conditional* recommendation is generally supported by lower-quality evidence or a close balance between desirable and undesirable outcomes. For a conditional recommendation, the recommended course of action would apply to the majority of the patients, but the alternative is a reasonable consideration. Conditional recommendations always warrant a shared decision-making approach. We specify conditions under which the alternative may be considered.

In some instances, the committee found that the evidence for a particular PICO question did not support a graded recommendation or did not favor one intervention over another. However, the Voting Panel believed that the PICO question addressed a commonly encountered clinical question which has not been fully clarified and requires further investigation, and thus felt that providing guidance for this question was warranted. For these situations, we present "ungraded position statements," which reflect general views of the Voting Panel.

In this evidence-based guideline, we explicitly used the best evidence available and present that in a transparent manner for the clinician reader/user (10). In some instances, this includes randomized trials in which the interventions under consideration are directly compared. The GRADE system rates evidence that comes exclusively from the collective experience of the Voting Panel and Patient Panel members as "very low–quality" evidence (15).

For each recommendation, details regarding the PICO questions and the GRADE evidence tables can be found in Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract).

RESULTS

For the GCA evidence report, 399 articles were reviewed to address 27 PICO questions. For the TAK evidence report, 347 articles were reviewed to address 27 PICO questions.

Table 1. Definitions of selected terms used in the recommendations and ungraded position statements for GCA and TAK*

Term	Definition
Disease states	
Suspected disease	Clinical signs and/or symptoms suggestive of GCA/TAK and not explained by other conditions
Active disease	New, persistent, or worsening clinical signs and/or symptoms attributed to GCA/TAK and not related to prior damage
Severe disease	Vasculitis with life- or organ-threatening manifestations (e.g., vision loss, cerebrovascular ischemia, cardiac ischemia, limb ischemia)
Nonsevere disease	Vasculitis without life- or organ-threatening manifestations (e.g., constitutional symptoms, headache, jaw claudication, symptoms of polymyalgia rheumatica)
Remission	Absence of clinical signs or symptoms attributed to active GCA/TAK, on or off immunosuppressive therapy
Refractory disease	Persistent active disease despite an appropriate course of immunosuppressive therapy
Relapse	Recurrence of active disease following a period of remission
Cranial ischemia	Visual and neurologic involvement including amaurosis fugax, vision loss, and stroke
Treatments	
IV pulse GCs	IV methylprednisolone 500–1,000 mg/day (adults) or 30 mg/kg/day (children; maximum 1,000 mg/day) or equivalent for 3–5 days
High-dose oral GCs	Prednisone 1 mg/kg/day up to 80 mg or equivalent
Moderate-dose oral GCs	Prednisone 0.5 mg/kg/day (generally 10–40 mg/day in adults) or equivalent
Low-dose oral GCs	Prednisone ≤10 mg/day or equivalent
Non-GC nonbiologic immunosuppressive therapy	Azathioprine, leflunomide, methotrexate, mycophenolate mofetil, cyclophosphamide
Biologics	Abatacept, tumor necrosis factor inhibitor, tocilizumab
Surgical intervention	Angioplasty, stent placement, vascular bypass, vascular graft
Disease assessments	
Clinical monitoring	Assessing for clinical signs and symptoms of active disease, obtaining 4 extremity blood pressures, and obtaining clinical laboratory results, including inflammation marker levels
Inflammation markers	Erythrocyte sedimentation rate, C-reactive protein level
Noninvasive imaging	Computed tomography angiogram, magnetic resonance angiogram, positron emission tomography scan, vascular ultrasound, magnetic resonance imaging of temporal and scalp arteries
Invasive imaging	Conventional catheter-based angiogram

* GCA = giant cell arteritis; TAK = Takayasu arteritis; IV = intravenous; GCs = glucocorticoids.

Recommendations and ungraded position statements for the management of GCA

Table 1 presents definitions of selected terms used in the recommendations, including disease states such as severe disease, dosing ranges for glucocorticoids, categorization of medications, and disease assessments. Tables 2 and 3 present the recommendations with their supporting PICO questions and levels of evidence. We present 22 recommendations and 2 ungraded position statements for GCA. All but 1 of the recommendations are conditional due to very low– to low-quality evidence. Figure 1 presents key recommendations for the treatment of GCA.

Diagnostic testing

Recommendation: For patients with suspected GCA, we conditionally recommend an initial unilateral temporal artery biopsy over bilateral biopsies.

Initially, a unilateral biopsy is recommended. However, bilateral temporal artery biopsies may be appropriate if the symptoms are not clearly localized to 1 temporal artery. Proceeding with the contralateral biopsy is also appropriate if the unilateral biopsy result is negative and additional evidence for cranial GCA is sought (17).

Recommendation: For patients with suspected GCA, we conditionally recommend a long-segment temporal artery biopsy specimen (>1 cm) over a short-segment temporal artery biopsy specimen (<1 cm).

A longer segment of the temporal artery is preferred, since GCA is a focal and segmental disease, and the added morbidity of obtaining a larger segment is very low. A shorter segment obtained on biopsy can result in reduced diagnostic yield and a missed diagnosis. This recommendation is conditional due to a lack of high-quality evidence, but the Voting Panel emphasized obtaining longer biopsy specimens when possible (18,19).

Recommendation: For patients with suspected GCA, we conditionally recommend obtaining a temporal artery biopsy specimen within 2 weeks of starting oral glucocorticoids over waiting longer than 2 weeks for a biopsy.

Overall, biopsy specimens should be obtained as soon as possible to maximize the likelihood of detecting histopathologic changes. Studies suggest that histopathologic changes indicating GCA are more likely to be detected in a temporal artery biopsy if obtained within 2 weeks of starting glucocorticoids; however, histopathologic changes have been detected in biopsy specimens obtained much later than 2 weeks after the start of glucocorticoid treatment (20–28). A biopsy specimen obtained 2 weeks after starting glucocorticoids could be informative and may be considered at the discretion of the physician and patient.

Recommendation: For patients with suspected GCA, we conditionally recommend temporal artery biopsy over temporal artery ultrasound for establishing a diagnosis of GCA.

In general, rheumatologists and radiologists in the US are less experienced in using ultrasound to diagnose temporal artery involvement in GCA compared to their counterparts in Europe. Therefore, temporal artery biopsy remains the optimal approach to diagnosing GCA in the US, because ultrasound is operator-dependent and results are influenced by treatment (i.e., signs of inflammation quickly disappear with glucocorticoid treatment). In centers with appropriate training and expertise in using temporal artery ultrasound, ultrasound may be a useful and complementary tool for diagnosing GCA (29–33).

Table 2. Recommendations for diagnostic testing in GCA*

Recommendation	GCA PICO question informing recommendation and discussion	Level of evidence
Recommendation: For patients with suspected GCA, we conditionally recommend an initial unilateral temporal artery biopsy over bilateral biopsies.	1	Low
Recommendation: For patients with suspected GCA, we conditionally recommend a long-segment temporal artery biopsy specimen (>1 cm) over a short-segment temporal artery biopsy specimen (<1 cm).	2	Low
Recommendation: For patients with suspected GCA, we conditionally recommend obtaining a temporal artery biopsy specimen within 2 weeks of starting oral GCs over waiting longer than 2 weeks for a biopsy.	3	Low
Recommendation: For patients with suspected GCA, we conditionally recommend temporal artery biopsy over temporal artery ultrasound for establishing a diagnosis of GCA.	4	Low
Recommendation: For patients with suspected GCA, we conditionally recommend temporal artery biopsy over MRI of the cranial arteries for establishing a diagnosis of GCA.	5	Low
Recommendation: For patients with suspected GCA and a negative temporal artery biopsy result (or results), we conditionally recommend noninvasive vascular imaging of the large vessels with clinical assessment to aid in diagnosis over clinical assessment alone.	6, 7	Very low to low
Recommendation: For patients with newly diagnosed GCA, we conditionally recommend obtaining noninvasive vascular imaging to evaluate large vessel involvement.	9	Very low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for giant cell arteritis (GCA), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract). GCs = glucocorticoids; MRI = magnetic resonance imaging.

Table 3. Recommendations/statements for treatment (medical management and surgical intervention) and clinical/laboratory monitoring in GCA*

Recommendation/statement	GCA PICO question informing recommendation and discussion	Level of evidence
Medical management		
Recommendation: For patients with newly diagnosed GCA without manifestations of cranial ischemia, we conditionally recommend initiating treatment with high-dose oral GCs over IV pulse GCs.	11	Very low to low
Recommendation: For patients with newly diagnosed GCA with threatened vision loss, we conditionally recommend initiating treatment with IV pulse GCs over high-dose oral GCs.	12	Very low
Recommendation: For patients with newly diagnosed GCA, we conditionally recommend dosing oral GCs daily over an alternate-day schedule.	18	Low
Recommendation: For patients with newly diagnosed GCA, we conditionally recommend initiating treatment with high-dose oral GCs over moderate-dose oral GCs.	14	Very low to low
Recommendation: For patients with newly diagnosed GCA, we conditionally recommend the use of oral GCs with tocilizumab over oral GCs alone.	15, 16, 17	Low to high
Recommendation: For patients with GCA with active extracranial large vessel involvement, we conditionally recommend treatment with oral GCs combined with a non-GC immunosuppressive agent over oral GCs alone.	21	Very low to low
Ungraded position statement: The optimal duration of therapy with GCs for GCA is not well established and should be guided by the patient's values and preferences.	20	Low to moderate
Recommendation: In patients with newly diagnosed GCA, we conditionally recommend *against* the use of an HMG-CoA reductase inhibitor ("statin") specifically for the treatment of GCA.	19	Very low
Recommendation: For patients with GCA who have critical or flow-limiting involvement of the vertebral or carotid arteries, we conditionally recommend adding aspirin.	13	Very low to moderate
Recommendation: For patients with GCA who experience disease relapse while receiving moderate-to-high–dose GCs, we conditionally recommend adding a non-GC immunosuppressive drug.	Relapse 2	†
Recommendation: For patients with GCA who experience disease relapse with symptoms of cranial ischemia, we conditionally recommend adding a non-GC immunosuppressive agent and increasing the dose of GCs over increasing the dose of GCs alone.	Relapse 1, 3	†
Recommendation: For patients with GCA who experience disease relapse with symptoms of cranial ischemia while receiving GCs, we conditionally recommend adding tocilizumab and increasing the dose of GCs over adding methotrexate and increasing the dose of GCs.	Relapse 4	†
Surgical intervention		
Ungraded position statement: For any patient requiring surgical vascular intervention for GCA, the type and timing of intervention should be a collaborative decision between the vascular surgeon and rheumatologist.	‡	‡
Recommendation: For patients with severe GCA and worsening signs of limb/organ ischemia who are receiving immunosuppressive therapy, we conditionally recommend escalating immunosuppressive therapy over surgical intervention with escalation of immunosuppressive therapy.	24	Very low to low
Recommendation: For patients with GCA undergoing vascular surgical intervention, we conditionally recommend the use of high-dose GCs during the periprocedural period, if the patient has active disease.	27	Very low
Clinical/laboratory monitoring		
Recommendation: For patients with GCA in apparent clinical remission, we strongly recommend long-term clinical monitoring over no clinical monitoring.	10	Very low to low
Recommendation: For patients with GCA who have an increase in levels of inflammation markers alone, we conditionally recommend clinical observation and monitoring without escalation of immunosuppressive therapy.	23	Very low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for giant cell arteritis (GCA), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract). GCs = glucocorticoids; IV = intravenous; HMG-CoA = hydroxymethylglutaryl-coenzyme A.
† PICO question was developed after completion of literature review and evidence reports. Data from studies already included in evidence reports were reviewed, but no dedicated literature review was performed for these questions. Recommendation was formed from available evidence and expert opinion.
‡ Ungraded position statement was not based on a specific PICO question.

Recommendation: For patients with suspected GCA, we conditionally recommend temporal artery biopsy over magnetic resonance imaging (MRI) of the cranial arteries for establishing a diagnosis of GCA.

Protocols to image the cranial vessels using different modalities, including MRI, have been developed, which can be helpful to establish a diagnosis of GCA (30,31,34–37). However, lack of technical expertise with this modality in the US, as well as the lack of widespread validation of this approach, limits the applicability of MRI with contrast of the cranial vessels as a replacement for temporal artery biopsy at the current time.

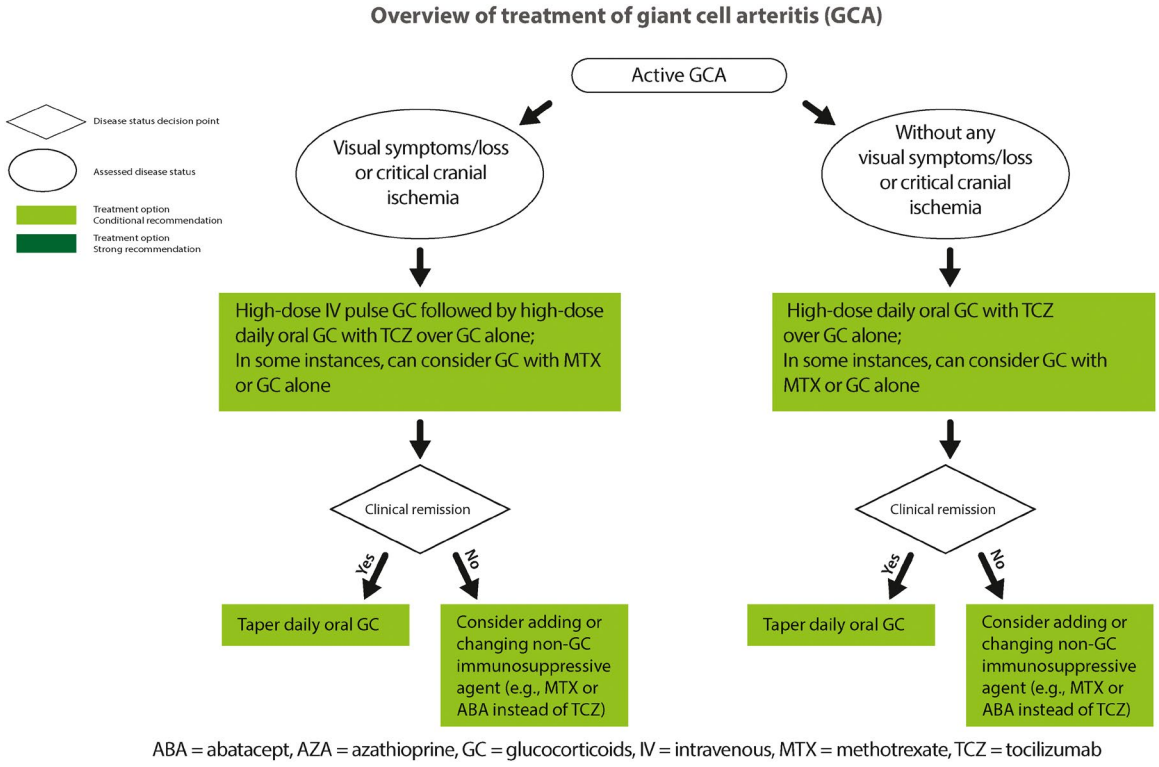
Overview of treatment of giant cell arteritis (GCA)
Disease status decision point
Assessed disease status
Treatment option
Conditional recommendation
Treatment option
Strong recommendation
Active GCA
Visual symptoms/loss or critical cranial ischemia
Without any visual symptoms/loss or critical cranial ischemia
High-dose IV pulse GC followed by high-dose daily oral GC with TCZ over GC alone; In some instances, can consider GC with MTX or GC alone
High-dose daily oral GC with TCZ over GC alone; In some instances, can consider GC with MTX or GC alone
Clinical remission
Clinical remission
Yes
No
Yes
No
Taper daily oral GC
Consider adding or changing non-GC immunosuppressive agent (e.g., MTX or ABA instead of TCZ)
Taper daily oral GC
Consider adding or changing non-GC immunosuppressive agent (e.g., MTX or ABA instead of TCZ)
ABA = abatacept, AZA = azathioprine, GC = glucocorticoids, IV = intravenous, MTX = methotrexate, TCZ = tocilizumab

Figure 1. Overview of treatment of giant cell arteritis.

Recommendation: For patients with suspected GCA and a negative temporal artery biopsy result (or results), we conditionally recommend noninvasive vascular imaging of the large vessels with clinical assessment to aid in diagnosis over clinical assessment alone.

Imaging the large vessels may provide additional evidence of disease (e.g., extracranial GCA) when the diagnosis is uncertain following negative temporal artery biopsy results (28,34,38–44). Potential diagnostic imaging modalities include MR or computed tomography (CT) angiography of the neck/chest/abdomen/pelvis, ultrasonography, and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) (43,45).

Recommendation: For patients with newly diagnosed GCA, we conditionally recommend obtaining noninvasive vascular imaging to evaluate large vessel involvement.

Baseline noninvasive imaging with MR or CT angiography of the neck/chest/abdomen/pelvis in patients with newly diagnosed GCA can detect large vessel involvement and may be compared with subsequent routine monitoring if indicated (46). In a patient with large vessel involvement, routine noninvasive vascular imaging can identify early and long-term complications, such as aneurysms and stenoses, and assess stability of existing lesions. In patients without large vessel involvement, routine and repeated monitoring with vascular imaging may or may not be necessary.

Medical management

Recommendation: For patients with newly diagnosed GCA without manifestations of cranial ischemia, we conditionally recommend initiating treatment with high-dose oral glucocorticoids over intravenous (IV) pulse glucocorticoids.

Cranial ischemic manifestations include visual and neurologic involvement such as amaurosis fugax, vision loss, and stroke. Some studies have suggested that the use of IV pulse glucocorticoids in this patient group could decrease disease relapse and increase remission rates. However, routine use of IV pulse glucocorticoids can also be associated with increased risks, including infections, that may outweigh the benefits, especially in the elderly (47,48).

Recommendation: For patients with newly diagnosed GCA with threatened vision loss, we conditionally recommend initiating treatment with IV pulse glucocorticoids over high-dose oral glucocorticoids.

Studies investigating the effect of IV pulse glucocorticoids in patients with GCA and cranial ischemia have demonstrated conflicting results. However, this population is at high risk for vision loss as well as toxicity from glucocorticoid use. IV pulse glucocorticoids can be used in patients with the highest risk of vision loss, but this decision should be guided by the patient's clinical condition, values, and preferences (49,50).

Recommendation: For patients with newly diagnosed GCA, we conditionally recommend dosing oral glucocorticoids daily over an alternate-day schedule.

This recommendation is conditional solely due to the low level of evidence, which indicates higher remission rates in patients receiving daily dosing. The panel did not identify any situations in which alternate-day dosing of prednisone would be preferred (51).

Recommendation: For patients with newly diagnosed GCA, we conditionally recommend initiating treatment with high-dose oral glucocorticoids over moderate-dose oral glucocorticoids.

We recommend starting high-dose oral glucocorticoids to achieve rapid disease control followed by tapering the glucocorticoid dose (weeks to months) to avoid prolonged high-dose treatment and reduce toxicity. The dosing and duration of oral glucocorticoid therapy can be variable depending on a patient's manifestations and comorbidities and whether the use of a glucocorticoid-sparing agent was also initiated. Studies supporting the efficacy and lower toxicity of moderate-dose glucocorticoids are of low quality, which prevents the Voting Panel from recommending moderate-dose glucocorticoids as initial therapy. Moderate-dose glucocorticoids may be used in patients with significant risk of severe glucocorticoid toxicity and in patients with low risk of vision loss or other life- or organ-threatening complications (48–53).

Recommendation: For patients with newly diagnosed GCA, we conditionally recommend the use of oral glucocorticoids with tocilizumab over oral glucocorticoids alone.

A trial published in 2017 (8) demonstrated that tocilizumab has a significant glucocorticoid-sparing effect in GCA, and thus, tocilizumab should be considered for initial treatment. However, methotrexate with glucocorticoids, as well as glucocorticoids alone, can also be considered as initial treatment for newly diagnosed GCA. The decision to treat with tocilizumab and glucocorticoids, methotrexate and glucocorticoids, or glucocorticoid monotherapy for initial therapy should be made based on the physician's experience and the patient's clinical condition, values, and preferences. Lack of long-term follow-up data on tocilizumab and cost may limit its use (8,54). Abatacept with glucocorticoids can also be considered if these other agents are not effective (55).

Recommendation: For patients with GCA with active extracranial large vessel involvement, we conditionally recommend treatment with oral glucocorticoids combined with a nonglucocorticoid immunosuppressive agent over oral glucocorticoids alone.

Management of GCA in patients with new, persistent, or worsening extracranial symptoms (e.g., limb claudication) or signs (e.g., imaging findings) attributed to GCA can include the addition of nonglucocorticoid immunosuppressive agents. These agents include biologic agents (e.g., tocilizumab) as well as oral therapies (e.g., methotrexate) (56,57). However, the Voting Panel recognizes that there are few high-quality studies evaluating the efficacy of these agents for this patient group. While there is stronger clinical evidence supporting the use of tocilizumab compared to methotrexate for the treatment of GCA, methotrexate can be considered for patients unable to use tocilizumab due to factors such as recurrent infections, history of gastrointestinal perforations or diverticulitis, and cost.

Ungraded position statement: The optimal duration of therapy with glucocorticoids for GCA is not well established and should be guided by the patient's values and preferences.

Factors that may influence the duration of therapy include the patient's clinical manifestations, toxicity related to glucocorticoid use, number of flares, the physician's experience, and the patient's preferences (8). Overall, the Patient Panel emphasized minimizing the use of glucocorticoids as much as possible but recognized that longer-term use may be needed in some patients to avoid flares.

Recommendation: In patients with newly diagnosed GCA, we conditionally recommend *against* the use of a hydroxymethylglutaryl-coenzyme A reductase inhibitor ("statin") specifically for the treatment of GCA.

The use of statins is not known to provide a clinically significant immunosuppressive effect for GCA. Whether statins are warranted to decrease the patient's risk of cardiovascular events is a separate clinical question and depends on the patient's risk factors for cardiovascular disease (58–60).

Recommendation: For patients with GCA who have critical or flow-limiting involvement of the vertebral or carotid arteries, we conditionally recommend adding aspirin.

There are few data regarding this clinical question, but the antiplatelet activity of aspirin may be beneficial in preventing ischemic events in patients with vascular narrowing causing decreased cerebral blood flow (61–64). The efficacy of aspirin to prevent ischemic events in patients without vertebral or carotid narrowing remains unclear at this time.

Recommendation: For patients with GCA who experience disease relapse while receiving moderate-to-high–dose glucocorticoids, we conditionally recommend adding a nonglucocorticoid immunosuppressive drug.

Relapses of any type while receiving moderate-to-high–dose glucocorticoids indicate that it is unlikely that it will be possible for glucocorticoids to be tapered to a low dose. Therefore, glucocorticoid-sparing therapy should be considered.

Recommendation: For patients with GCA who experience disease relapse with symptoms of cranial ischemia, we conditionally recommend adding a nonglucocorticoid immunosuppressive agent and increasing the dose of glucocorticoids over increasing the dose of glucocorticoids alone.

Nonglucocorticoid immunosuppressive agents considered in this situation include tocilizumab and methotrexate (8,65,66). Relapses with symptoms of polymyalgia rheumatica may be controlled by increasing the dose of glucocorticoids alone.

Recommendation: For patients with GCA who experience disease relapse with cranial symptoms while receiving glucocorticoids, we conditionally recommend adding tocilizumab and increasing the dose of glucocorticoids over adding methotrexate and increasing the dose of glucocorticoids.

Tocilizumab is an effective glucocorticoid-sparing agent for GCA (8,54). While there are no comparative studies, the glucocorticoid-sparing effect seen with methotrexate is smaller than the effect seen with tocilizumab (8,55,65–67). While the glucocorticoid-sparing effect of tocilizumab is best quantified using the subcutaneous formulation (8), IV tocilizumab has also been shown to be glucocorticoid-sparing (54). Again, methotrexate can be considered for patients who are unable to tolerate or have limited access to tocilizumab.

Surgical intervention

Ungraded position statement: For any patient requiring surgical vascular intervention for GCA, the type and timing of intervention should be a collaborative decision between the vascular surgeon and rheumatologist.

Recommendation: For patients with severe GCA and worsening signs of limb/organ ischemia who are receiving immunosuppressive therapy, we conditionally recommend escalating immunosuppressive therapy over surgical intervention with escalation of immunosuppressive therapy.

Because patients can develop collateral blood vessels to improve distal blood flow, immunosuppressive therapy is recommended as initial therapy in patients with GCA and worsening limb/organ ischemia. However, clinical situations that would warrant consideration of immediate surgical intervention include aortic aneurysms at high risk for rupture and impending/progressive tissue or organ infarction or damage (68–70).

Recommendation: For patients with GCA undergoing vascular surgical intervention, we conditionally recommend the use of high-dose glucocorticoids during the periprocedural period, if the patient has active disease.

This recommendation pertains to patients with GCA who are undergoing a vascular surgical intervention due to a complication of GCA (e.g., aneurysm or stenosis). There are limited data regarding the use of high-dose glucocorticoids during the periprocedural period in GCA, and thus, support for this recommendation is based in part on their use in TAK. As in TAK, high doses of oral glucocorticoids in the perioperative setting are recommended if the disease is active or if the clinician is concerned that the patient may have active disease.

Clinical/laboratory monitoring

Recommendation: For patients with GCA in apparent clinical remission, we strongly recommend long-term clinical monitoring over no clinical monitoring.

The optimal frequency and length of monitoring are not well established and depend on factors including the duration of remission, site of involvement, risk of disease progression, whether the patient is receiving immunosuppressive therapy, and reliability of the patient to report new signs or symptoms (48,69). Clinical monitoring may include history taking, examinations, and laboratory and imaging studies. This is a strong recommendation given the minimal risks and potential catastrophic outcomes if monitoring is not performed.

Recommendation: For patients with GCA who have an increase in levels of inflammation markers alone, we conditionally recommend clinical observation and monitoring without escalation of immunosuppressive therapy.

Increases in levels of inflammation markers such as erythrocyte sedimentation rate and C-reactive protein can be nonspecific (69). Therefore, increasing immunosuppressive therapy is not warranted in the setting of increased levels of inflammation markers in the absence of other signs of disease activity. However, these increased levels may warrant more frequent clinical and/or radiographic assessments for active disease.

Recommendations and ungraded position statement for the management of TAK

Table 1 presents definitions of selected terms used in the recommendations, and Tables 4 and 5 present the recommendations with their supporting PICO questions and levels of evidence. We present 20 recommendations and 1 ungraded position statement for TAK. All recommendations except for 1 are conditional due to the availability of only very low– to low-quality evidence. Figure 2 presents key recommendations for the treatment of TAK.

Medical management

Recommendation: For patients with active, severe TAK who are not receiving immunosuppressive therapy, we conditionally recommend initiating treatment with high-dose oral glucocorticoids over IV pulse glucocorticoids followed by high-dose oral glucocorticoids.

There is no evidence that IV pulse glucocorticoids are more effective than high-dose oral glucocorticoids in this setting.

IV pulse glucocorticoids may be considered for patients with life- or organ-threatening disease. In children, alternate steroid dosing regimens (e.g., IV pulse glucocorticoids with low daily oral dosing) may be preferred to improve compliance and potentially reduce adverse consequences such as impacting growth (71).

Recommendation: For patients with newly active, severe TAK, we conditionally recommend initiating treatment with high-dose glucocorticoids over low-dose glucocorticoids.

A higher dose of glucocorticoids is recommended due to the potential for organ damage or life-threatening events. However, lower doses of glucocorticoids may be considered for patients with newly active, nonsevere disease (e.g., patients with constitutional symptoms and without limb ischemia) (72).

Recommendation: For patients with TAK who achieved remission while receiving glucocorticoids for ≥6–12 months, we conditionally recommend tapering off glucocorticoids over long-term treatment with low-dose glucocorticoids for remission maintenance.

The optimal duration of glucocorticoid use in TAK is unknown. Glucocorticoid exposure should be limited if possible in order to minimize toxicity. Glucocorticoids may be continued for a longer duration if disease is not adequately controlled or if the patient experiences frequent disease relapse.

Table 4. Recommendations/statement for treatment (medical management and surgical intervention) in TAK*

Recommendation/statement	TAK PICO question informing recommendation and discussion	Level of evidence
Medical management		
Recommendation: For patients with active, severe TAK who are not receiving immunosuppressive therapy, we conditionally recommend initiating treatment with high-dose oral GCs over IV pulse GCs followed by high-dose oral GCs.	6	Very low
Recommendation: For patients with newly active, severe TAK, we conditionally recommend initiating treatment with high-dose GCs over low-dose GCs.	5	Very low to low
Recommendation: For patients with TAK who achieved remission while receiving GCs for ≥6–12 months, we conditionally recommend tapering off GCs over long-term treatment with low-dose GCs for remission maintenance.	15	Very low
Recommendation: For patients with active TAK, we conditionally recommend the use of a non-GC immunosuppressive agent plus GCs over GCs alone.	7, 8, 9	Low
Recommendation: For patients with active TAK, we conditionally recommend the use of other non-GC immunosuppressive therapy over tocilizumab as initial therapy.	8, 10, 11, 12	Very low to low
Recommendation: For patients with TAK that is refractory to treatment with GCs alone, we conditionally recommend adding a tumor necrosis factor inhibitor over adding tocilizumab.	14	Very low
Recommendation: For patients with TAK and asymptomatic progression of a previously identified vascular lesion seen on imaging, without evidence of inflammation, we conditionally recommend continuing current therapy over escalating/changing immunosuppressive therapy.	16	Very low
Recommendation: For patients with active TAK and critical cranial or vertebrobasilar involvement, we conditionally recommend adding aspirin or another antiplatelet therapy.	13	Low
Surgical intervention		
Ungraded position statement: For any patient requiring surgical vascular intervention, the type and timing of intervention should be a collaborative decision between the vascular surgeon and rheumatologist.	†	†
Recommendation: In patients with known TAK and persistent limb claudication without evidence of ongoing active disease, we conditionally recommend *against* surgical intervention.	20	Very low to low
Recommendation: For patients with known TAK with worsening signs of limb/organ ischemia while receiving immunosuppressive therapy, we conditionally recommend escalating immunosuppressive therapy over surgical intervention with escalation of immunosuppressive therapy.	21, 24	Very low
Recommendation: For patients with TAK with renovascular hypertension and renal artery stenosis, we conditionally recommend medical management over surgical intervention.	26	Very low to low
Recommendation: For patients with TAK and stenosis of a cranial/cervical vessel without clinical symptoms, we conditionally recommend medical management over surgical intervention.	22	Very low to low
Recommendation: For patients with TAK with worsening signs of limb/organ ischemia, we conditionally recommend delaying surgical intervention until the disease is quiescent over performing surgical intervention while the patient has active disease.	23	Very low to low
Recommendation: For patients with TAK who are undergoing surgical intervention, we conditionally recommend the use of high-dose GCs in the periprocedure period if the patient has active disease.	25	Very low to low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for Takayasu arteritis (TAK), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract). GCs = glucocorticoids; IV = intravenous.
† Ungraded position statement was not based on a specific PICO question.

Table 5. Recommendations for clinical/laboratory monitoring and vascular imaging in TAK*

Recommendation	TAK PICO question informing recommendation and discussion	Level of evidence
Clinical/laboratory monitoring		
Recommendation: For patients with TAK, we conditionally recommend adding inflammation markers to clinical monitoring as a disease activity assessment tool.	2	Very low to low
Recommendation: For patients with TAK in apparent clinical remission, we strongly recommend long-term clinical monitoring over no clinical monitoring.	4	Very low
Recommendation: For patients with TAK in apparent clinical remission but with an increase in levels of inflammation markers, we conditionally recommend clinical observation without escalation of immunosuppressive therapy.	19	Very low
Vascular imaging		
Recommendation: For patients with TAK, we conditionally recommend the use of noninvasive imaging over catheter-based dye angiography as a disease activity assessment tool.	1	Low
Recommendation: For patients with known TAK, we conditionally recommend regularly scheduled noninvasive imaging in addition to routine clinical assessment.	3	Very low to low
Recommendation: For patients with TAK in apparent clinical remission but with signs of inflammation in new vascular territories (e.g., new stenosis or vessel wall thickening) on vascular imaging, we conditionally recommend treatment with immunosuppressive therapy.	17, 18	Very low to low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for Takayasu arteritis (TAK), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract).

Recommendation: For patients with active TAK, we conditionally recommend the use of a nonglucocorticoid immunosuppressive agent plus glucocorticoids over glucocorticoids alone.

Nonglucocorticoid immunosuppressive agents are recommended over monotherapy with glucocorticoids to minimize glucocorticoid-related toxicity. Methotrexate is often used as the initial nonglucocorticoid immunosuppressive agent, but other therapies such as tumor necrosis factor inhibitors and azathioprine can be considered as well (70–73). Methotrexate is often preferred for use in children since it is usually well tolerated. Glucocorticoid monotherapy can be considered for mild disease or if the diagnosis is uncertain.

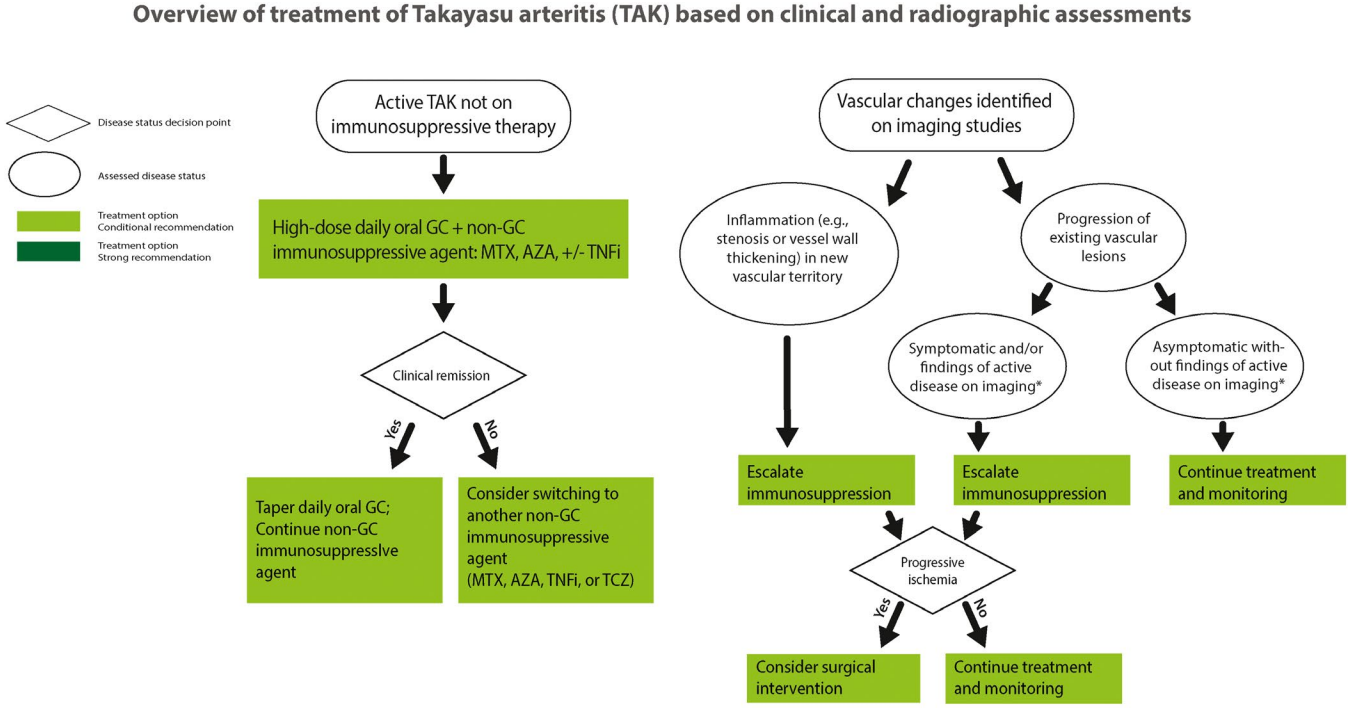
Overview of treatment of Takayasu arteritis (TAK) based on clinical and radiographic assessments
Disease status decision point
Assessed disease status
Treatment option
Conditional recommendation
Treatment option
Strong recommendation
Active TAK not on immunosuppressive therapy
High-dose daily oral GC + non-GC immunosuppressive agent: MTX, AZA, +/- TNFi
Clinical remission
Yes
No
Taper daily oral GC; Continue non-GC immunosuppresslve agent
Consider switching to another non-GC immunosuppressive agent (MTX, AZA, TNFi, or TCZ)
Vascular changes identified on imaging studies
Inflammation (e.g., stenosis or vessel wall thickening) in new vascular territory
Progression of existing vascular lesions
Symptomatic and/or findings of active disease on imaging*
Asymptomatic without findings of active disease on imaging*
Escalate immunosuppression
Escalate immunosuppression
Continue treatment and monitoring
Progressive ischemia
Yes
No
Consider surgical intervention
Continue treatment and monitoring
AZA = azathioprine; CT = computed tomography; FDG-PET = 18F-fluorodeoxyglucose positron emission tomography; GC = glucocorticoids; MR = magnetic resonance; MTX = methotrexate; TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor
* Can be suggested by vascular edema, contrast enhancement, and/or increased wall thickness on MR or CT angiography, or supra-physiologic FDG uptake in the arterial wall on PET imaging

Figure 2. Overview of treatment of Takayasu arteritis based on clinical and radiographic assessments.

Patient-specific factors such as alcohol use, plans for childbearing, medication compliance, and medical comorbidities may influence the choice of immunosuppressant (73,74).

Recommendation: For patients with active TAK, we conditionally recommend the use of other nonglucocorticoid immunosuppressive therapy over tocilizumab as initial therapy.

As discussed above, nonglucocorticoid immunosuppressive agents such as methorexate, tumor necrosis factor inhibitors, and azathioprine can be used as initial therapy in TAK. We recommend these agents over tocilizumab for initial therapy, because the efficacy of tocilizumab in TAK is not established at this time. While tocilizumab has been shown to be efficacious for GCA, the primary efficacy end point was not achieved in the only randomized trial of tocilizumab in TAK conducted thus far (74,75). Tocilizumab may be considered for patients with inadequate response to other immunosuppressive therapies. Abatacept is not recommended, since it has been shown in a small randomized controlled trial to not be efficacious in TAK (74,76).

Recommendation: For patients with TAK that is refractory to treatment with glucocorticoids alone, we conditionally recommend adding a tumor necrosis factor inhibitor over adding tocilizumab.

We recognize that among biologic therapies, some practitioners favor TNF inhibition, while others favor interleukin-6 inhibition (tocilizumab) in this situation. Overall, the Voting Panel favored tumor necrosis factor inhibitors over tocilizumab, since there is more clinical experience with and data on tumor necrosis factor inhibitors in TAK compared to tocilizumab. In observational studies, tumor necrosis factor inhibitors have been shown to induce remission and decrease relapses (77–79). Clinical experience with tocilizumab in TAK has been demonstrated in a randomized controlled trial and small case series. In the randomized trial, a trend toward a longer time to relapse was seen in the tocilizumab arm, but the difference was not statistically significant. However, that study was felt to be underpowered (36 participants). Of note, tocilizumab use also affects acute-phase reactants, which may impact ability to gauge disease activity. Therefore, while the panel favors tumor necrosis factor inhibitor use, we recognize that tocilizumab may also be considered, especially when tumor necrosis factor inhibitors are contraindicated (75).

Recommendation: For patients with TAK and asymptomatic progression of a previously identified vascular lesion seen on imaging, without evidence of inflammation, we conditionally recommend continuing current therapy over escalating/changing immunosuppressive therapy.

Vascular lesions can progress due to a number of factors that may not be related to active disease, such as "healing fibrosis" in response to effective treatment. Intervention is not always needed, since collateral circulation frequently develops over time. However, the location and the extent of the lesion of the affected vessel should be considered. Escalating immunosuppressive therapy may be warranted if significant progression has developed rapidly (e.g., weeks to months) after a period of stable disease (80,81).

Recommendation: For patients with active TAK and critical cranial or vertebrobasilar involvement, we conditionally recommend adding aspirin or another antiplatelet therapy.

Small observational studies suggest a decreased risk of ischemic events with antiplatelet therapy but an increased risk of bleeding (82). Therefore, antiplatelet therapy is usually used for patients at higher risk of ischemic events (e.g., patients with flow-limiting vertebrobasilar disease or stents). Antiplatelet therapy should be used with caution after surgical procedures or if there is an increased risk of bleeding (81).

Clinical/laboratory monitoring

Recommendation: For patients with TAK, we conditionally recommend adding inflammation markers to clinical monitoring as a disease activity assessment tool.

While inflammation markers are an imperfect indicator of disease activity, they may be helpful for clinical monitoring (80,83).

Recommendation: For patients with TAK in apparent clinical remission, we strongly recommend long-term clinical monitoring over no clinical monitoring.

The frequency of monitoring depends on factors including the duration of remission, sites of involvement, risk of disease progression, the patient's immunosuppressive regimen, and the ability and likelihood of the patient reliably reporting new signs or symptoms of TAK. This is a strong recommendation given the minimal risks and potential catastrophic outcomes without monitoring (80,83).

Recommendation: For patients with TAK in apparent clinical remission but with an increase in levels of inflammation markers, we conditionally recommend clinical observation without escalation of immunosuppressive therapy.

As discussed above in the GCA recommendations, increases in levels of inflammation markers can be nonspecific, and intensifying immunosuppressive therapy in the setting of increased inflammation markers alone may not be warranted. More frequent clinical and/or radiographic assessments for active disease can be considered (77,80,83).

Vascular imaging

Recommendation: For patients with TAK, we conditionally recommend the use of noninvasive imaging over catheter-based dye angiography as a disease activity assessment tool.

Noninvasive imaging such as CT angiography, MR angiography, or FDG-PET are recommended because these imaging modalities provide information regarding vascular wall inflammation, while catheter-based angiography primarily provides information regarding the vascular lumen. Catheter-based angiography can be used to accurately determine central blood pressures, as part of surgical planning, or if noninvasive modalities do not provide adequate information. Identifying active disease based on noninvasive imaging at this time can be challenging, since the hallmarks of active disease have not been definitively established (43,45,84).

Recommendation: For patients with known TAK, we conditionally recommend regularly scheduled noninvasive imaging in addition to routine clinical assessment.

Routine imaging is recommended since vascular changes in TAK can occur when the disease is considered clinically quiescent. The optimal interval between imaging studies is not well established, and ranges vary (e.g., every 3–6 months or longer). The interval may be shorter early in the disease course and longer with established, quiescent disease. Since sedation may be required for imaging studies in children and can be associated with potential risks and complications, routine imaging of inactive disease in children is at the discretion of the treating clinician, while considering risks and benefits (85,86).

Recommendation: For patients with TAK in apparent clinical remission but with signs of inflammation in new vascular territories (e.g., new stenosis or vessel wall thickening) on vascular imaging, we conditionally recommend treatment with immunosuppressive therapy.

A new arterial stenosis is concerning as it can indicate recent active disease, and thus usually warrants immunosuppressive therapy. Other findings suggestive of active disease on MR angiography or CT angiography include vascular edema, contrast enhancement, and increased wall thickness, and may result in luminal damage over time. Findings of active disease by FDG-PET are defined by supraphysiologic FDG uptake in the arterial wall. However, abnormal findings in the vascular wall identified by imaging are not necessarily specific to vascular inflammation. The implication of finding vessel wall edema or enhancement on imaging remains an area of investigation, and the clinical importance of such findings on CT angiography, MR angiography, or FDG-PET is not certain (43,45,80,83–86). Therefore, all therapeutic decision-making in this context should occur after reviewing the imaging findings with a radiologist to help determine whether the observed imaging changes represent active disease.

Surgical intervention

Ungraded position statement: For any patient requiring surgical vascular intervention, the type and timing of intervention should be a collaborative decision between the vascular surgeon and rheumatologist.

Recommendation: In patients with known TAK and persistent limb claudication without evidence of ongoing active disease, we conditionally recommend *against* surgical intervention.

Patients with TAK can develop collateral circulation that bypasses the stenosis causing limb claudication, and thus, surgical intervention may not be needed (87). However, surgical intervention can be considered for patients whose activities are significantly impacted by limb claudication.

Recommendation: For patients with known TAK with worsening signs of limb/organ ischemia while receiving immunosuppressive therapy, we conditionally recommend escalating immunosuppressive therapy over surgical intervention with escalation of immunosuppressive therapy.

Immunosuppressive therapy is recommended to control vascular inflammation in order to improve or prevent worsening blood flow. However, clinical situations that could warrant immediate surgical intervention include coronary artery involvement and impending/progressive tissue or organ infarction (88–90).

Recommendation: For patients with TAK with renovascular hypertension and renal artery stenosis, we conditionally recommend medical management over surgical intervention.

Medical management includes antihypertensive drugs and immunosuppressive therapy if TAK is active. Surgical intervention (including catheter-based interventions) may be warranted for hypertension that is refractory to medical management in spite of optimized immunosuppressive therapy or in the setting of worsening renal function (12,91–94).

Recommendation: For patients with TAK and stenosis of a cranial/cervical vessel without clinical symptoms, we conditionally recommend medical management over surgical intervention.

Medical therapy is recommended if only a single vessel is involved, due to the substantial risks of surgery. Surgical interventions can be considered if multiple vessels are involved. This recommendation is based on indirect evidence obtained from neurologic experience and studies, because there is no direct evidence for TAK (90,95–98).

Recommendation: For patients with TAK with worsening signs of limb/organ ischemia, we conditionally recommend delaying surgical intervention until the disease is quiescent over performing surgical intervention while the patient has active disease.

Observational studies have suggested improved outcomes if surgical intervention is performed when disease is not active. However, surgical intervention during active disease may be necessary if the patient has life- or organ-threatening manifestations such as stroke, loss of viability of a limb, or myocardial ischemia (99–101). We recognize that determining the level of disease activity in TAK can be challenging.

Recommendation: For patients with TAK who are undergoing surgical intervention, we conditionally recommend the use of high-dose glucocorticoids in the periprocedure period if the patient has active disease.

This recommendation pertains to patients with TAK who are undergoing a vascular surgical intervention due to a complication of TAK. High doses of oral glucocorticoids in the perioperative setting are recommended if the disease is active or if the clinician is concerned that the patient may have active disease (90,96,102).

DISCUSSION

This guideline presents the ACR/Vasculitis Foundation recommendations for the use of diagnostic testing, treatment, clinical and laboratory monitoring, and surgical intervention for patients with GCA or TAK. Overarching themes of the recommendations include the preference, in the US, for temporal artery biopsy over cranial imaging studies for the diagnosis of GCA, the use of large vessel imaging for GCA and TAK for diagnosis and disease monitoring, and limiting glucocorticoid exposure in order to minimize toxicity. Almost all recommendations are conditional due to low-quality evidence, reflecting the paucity of randomized clinical trials in these diseases.

Our recommendations regarding the use of temporal artery imaging differ from those presented by the European Alliance of Associations for Rheumatology (EULAR). In its recommendations regarding the use of imaging in large vessel vasculitis, EULAR indicates that the diagnosis of GCA may be made with a positive imaging test (e.g., temporal artery ultrasound or MRI of the cranial vessels), without additional testing such as temporal artery biopsy (103). However, the imaging recommendations presented by EULAR assume adequate expertise with these modalities. In the US, there is limited experience with temporal artery ultrasound and MRI of the cranial vessels as a diagnostic replacement for temporal artery biopsy, and thus, we continue to recommend temporal artery biopsy as the diagnostic test of choice at this time. However, we hope and anticipate that as experience with imaging of the temporal arteries to detect GCA (e.g., temporal artery ultrasound, MRI, and/or FDG-PET) increases in the US, patients will be able to benefit from these diagnostic tests. Also, in contrast to EULAR, we favor initial treatment of GCA with glucocorticoids and a glucocorticoid-sparing agent, given the well-recognized toxicity of glucocorticoids (104,105).

When reviewing the data abstracted for the PICO questions, it was clear that many critical clinical questions remain unanswered for GCA and TAK, and the lack of sufficient clinical evidence for these questions is reflected in the ungraded position statements presented in this guideline. For example, the optimal duration of therapy for any treatment and how best to monitor disease status is unknown. Few glucocorticoid-sparing agents have been identified through high-quality data. Accurate and validated indicators of disease activity have not been established or widely used for GCA or TAK. Interpretation of imaging studies in GCA and TAK can be challenging, and the clinical significance of persistent vascular wall inflammation during clinically quiescent disease is unclear.

Given these critical gaps in knowledge, we encourage additional research into the management of GCA and TAK. Studies that may greatly benefit patient care include the following: 1) translational studies contributing to the understanding of disease pathogenesis to facilitate development of more targeted therapies; 2) randomized clinical trials identifying new therapeutic options for the management of GCA and TAK; 3) randomized clinical trials comparing the effectiveness of currently used immunosuppressive therapies; and 4) longitudinal studies with biospecimen collection and routine vascular imaging to identify biomarkers of disease activity, indicators of disease prognosis, and the clinical sequelae of abnormalities identified on vascular imaging. We are hopeful that additional investigations into GCA and TAK will enable a more tailored approach to disease management in order to improve outcomes and minimize treatment toxicities.

ACKNOWLEDGMENTS

We thank Anne M. Ferris, MBBS, Ora Gewurz-Singer, MD, Rula Hajj-Ali, MD, Eric Matteson, MD, MPH, Robert F. Spiera, MD, Linda Wagner-Weiner, MD, MS, and Kenneth J. Warrington, MD, for serving on the Expert Panel. We thank Antoine G. Sreih, MD and Gary S. Hoffman, MD, MS, for their contributions during the early phases of this project as members of the Core Team. Dr. Hoffman's participation ended July 2018 due to personal reasons. Dr. Sreih's involvement ended in December 2018 when he became primarily employed by industry, which precluded his continued participation in this project. We thank Joyce Kullman (Vasculitis Foundation) for her assistance with recruitment for the Patient Panel. We thank the patients who (along with authors Kathy A. Full and Omar I. Vitobaldi) participated in the Patient Panel meeting: Jane Ascroft, Scott A. Brunton, Dedra DeMarco, Thomas Fitzpatrick, Jenn Gordon, Maria S. Mckay, Sandra Nye, Stephanie Sakson, and Ben Wilson. We thank Robin Arnold, Catherine E. Najem, MD, MSCE, and Amit Aakash Shah, MD, MPH, for their assistance with the literature review. We thank the ACR staff, including Ms Regina Parker, for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, and Ms Robin Lane for assistance in manuscript preparation. We thank Ms Janet Waters for help in developing the literature search strategy and performing the initial literature search, and Ms Janet Joyce for performing the update searches.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Maz, Chung, and Abril had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Maz, Chung, Langford, Abril, Gorelik, Archer, Conn, Full, Grayson, Ibarra, Imundo, Kim, Merkel, Rhee, Seo, Stone, Vitobaldi, Warner, Byram, Dua, Husainat, Kalot, Lin, Springer, Turgunbaev, Mustafa.

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Arthritis & Rheumatology
Vol. 0, No. 0, Month 2022, pp 1–9
DOI 10.1002/art.42325
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2022 American College of Rheumatology/EULAR Classification Criteria for Giant Cell Arteritis

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the EULAR Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

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Objective. To develop and validate updated classification criteria for giant cell arteritis (GCA).

Methods. Patients with vasculitis or comparator diseases were recruited into an international cohort. The study proceeded in 6 phases: 1) identification of candidate items, 2) prospective collection of candidate items present at the time of diagnosis, 3) expert panel review of cases, 4) data-driven reduction of candidate items, 5) derivation of a points-based risk classification score in a development data set, and 6) validation in an independent data set.

Results. The development data set consisted of 518 cases of GCA and 536 comparators. The validation data set consisted of 238 cases of GCA and 213 comparators. Age ≥50 years at diagnosis was an absolute requirement for classification. The final criteria items and weights were as follows: positive temporal artery biopsy or temporal artery halo sign on ultrasound (+5); erythrocyte sedimentation rate ≥50 mm/hour or C-reactive protein ≥10 mg/liter (+3); sudden visual loss (+3); morning stiffness in shoulders or neck, jaw or tongue claudication, new temporal headache, scalp tenderness, temporal artery abnormality on vascular examination, bilateral axillary involvement on imaging, and fluorodeoxyglucose–positron emission tomography activity throughout the aorta (+2 each). A patient could be classified as having GCA with a cumulative score of ≥6 points. When these criteria were tested in the validation data set, the model area under the curve was 0.91 (95% confidence interval [95% CI] 0.88–0.94) with a sensitivity of 87.0% (95% CI 82.0–91.0%) and specificity of 94.8% (95% CI 91.0–97.4%).

Conclusion. The 2022 American College of Rheumatology/EULAR GCA classification criteria are now validated for use in clinical research.

This article is published simultaneously in *Annals of the Rheumatic Diseases*.

The Diagnostic and Classification Criteria in Vasculitis (DCVAS) study, which included the development of this classification criteria, was funded by grants from the American College of Rheumatology (ACR), EULAR, the Vasculitis Foundation, and the University of Pennsylvania Vasculitis Center. This study was also supported by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH.

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INTRODUCTION

Giant cell arteritis (GCA), formerly known as temporal arteritis, is the most common form of systemic vasculitis in patients aged ≥50 years (1). GCA is defined by granulomatous arteritis that affects large- and medium-sized blood vessels with a predisposition to affect the cranial arteries (2). Common presenting features of the disease include headache, constitutional symptoms, jaw claudication, scalp tenderness, visual disturbances, and elevated inflammatory markers (3).

In 1990, the American College of Rheumatology (ACR) endorsed classification criteria for GCA (4). These criteria were established before the widespread use of noninvasive and advanced vascular imaging modalities, which have become increasingly incorporated in the clinical assessment of GCA. Vascular ultrasound can be used to diagnose GCA, and depending on the clinical setting, a noncompressible "halo" sign of a temporal ± axillary artery may replace the need for temporal artery biopsy (TAB) (5–8). Moreover, vascular imaging has demonstrated that arterial involvement in GCA is not exclusively confined to the cranial arteries (9,10) and can commonly affect the aorta and primary branches in a pattern similar to Takayasu arteritis (TAK) (11,12).

The limitations of the ACR 1990 criteria for GCA have become more apparent in the conduct of recent clinical trials and other research studies, in which investigators typically modify the 1990 ACR criteria to reflect modern practice (6,13,14). Notably, the 1990 ACR criteria focus mostly on cranial features of GCA and do not perform well in classifying patients with disease predominantly affecting the larger arteries. The 1990 ACR criteria were derived using comparator populations which included many patients with small-vessel vasculitis, a form of vasculitis that is not typically difficult to differentiate from GCA. In addition, the 1990 ACR criteria for GCA followed the "number of criteria" rule, which considered each criterion to have equal weight as a classifier for the disease. Since then, methodologic advances in classification criteria have allowed movement toward weighted criteria with threshold scores that improve performance characteristics (15,16).

This article outlines the development and validation of the revised ACR/EULAR–endorsed classification criteria for GCA.

METHODS

An international Steering Committee comprising clinician investigators with expertise in vasculitis, statisticians, and data managers was assembled to oversee the overall development of classification criteria for primary vasculitis (17). A detailed and complete description of the methods involved in the development and validation of the classification criteria for GCA is located in the Supplementary Appendix 1 (http://onlinelibrary.wiley.com/doi/10.1002/art.42325). Briefly, the Steering Committee implemented a 6-stage plan using data-driven and consensus methodology to develop the following criteria.

Stage 1: generation of candidate classification items for the systemic vasculitides. Candidate classification items were generated by expert opinion and reviewed by a group of vasculitis experts across a range of specialties using nominal group technique.

Stage 2: Diagnostic and Classification Criteria for Vasculitis (DCVAS) prospective observational study. A prospective, international, multisite observational study was conducted (see Appendix A for study investigators and sites). Ethical approval was obtained from local ethics committees. Consecutive patients representing the full spectrum of vasculitides were recruited from academic and community practices. Patients were included if they were 18 years or older and had a diagnosis of vasculitis or a condition that mimics vasculitis (e.g., infection, malignancy, atherosclerosis). Patients with GCA could only be enrolled within 2 years of diagnosis. Only data present at diagnosis were used to develop the classification criteria.

Stage 3: expert review to derive a gold standard–defined set of cases of large-vessel vasculitis (LVV). Experts in vasculitis from a wide range of geographic locations and specialties (see Appendix A) reviewed all submitted cases of vasculitis and a random selection of vasculitis mimics. Each reviewer was asked to review ~50 submitted cases to confirm the diagnosis and to specify the degree of certainty of their diagnosis as follows: very certain, moderately certain, uncertain, or very uncertain. Only cases agreed upon with at least moderate certainty by 2 reviewers were retained for further analysis.

Stage 4: refinement of candidate items specifically for LVV. The Steering Committee conducted a data-driven process to reduce the number of candidate items of relevance to cases and comparators for LVV. Density plots were assessed to study age distribution at diagnosis and symptom onset for GCA

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.42325&file=art42325-sup-0001-Disclosureform.pdf.

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Submitted for publication February 14, 2022; accepted in revised form July 30, 2022.

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and TAK. Absolute age requirements versus incorporation of age as a candidate criteria item was considered. Items related to the vascular physical examination, vascular imaging, arterial biopsy, and laboratory values were combined or eliminated based on consensus review. Items were selected for exclusion if they had a prevalence of <5% within the data set, and/or they were not clinically relevant for classification criteria (e.g., related to infection, malignancy, or demography). Low-frequency items of clinical importance could be combined, when appropriate. Patterns of vascular imaging findings detected by vascular ultrasound, angiography, or positron emission tomography (PET) were defined by K-means clustering (18).

Stage 5: derivation of the final classification criteria for GCA. The DCVAS data set was split into development (70%) and validation (30%) sets. Comparisons were performed between cases of GCA and a randomly selected comparator group in the following proportions: TAK, 33.5%; other vasculitides that mimic GCA and TAK (isolated aortitis, primary central nervous system vasculitis, polyarteritis nodosa, Behçet's disease, and other LVV), 33.4%; and other diagnoses that mimic LVV (e.g., atherosclerosis, unspecific headache), 33.1%. Least absolute shrinkage and selection operator (lasso) logistic regression was used to identify predictors from the data set and create a parsimonious model including only the most important predictors (19). The final items in the model were formulated into a clinical risk-scoring tool, with each factor assigned a weight based on its respective regression coefficient. A threshold that best balanced sensitivity and specificity was identified for classification.

Stage 6: validation of the final classification criteria for GCA. Performance of the new criteria was validated in an independent set of cases and comparators. Performance of the final classification criteria was examined in specific subsets of patients with GCA using data from the combined development and validation sets to maximize sample sizes for the subgroups. Patients were studied according to different disease subtypes (biopsy-proven GCA and large-vessel GCA) and regions of the world (North America, Europe) where clinical strategies to assess GCA are known to differ (20). Biopsy-proven GCA was defined as definite vasculitis on TAB reported by the submitting physician, and large-vessel GCA was defined as vasculitic involvement of the aorta or its branch arteries on either angiography (computed tomography, magnetic resonance imaging, or catheter-based angiography), ultrasound, or PET, without vasculitis on TAB. Comparison was made between the measurement properties of the new classification criteria for GCA and the 1990 ACR classification criteria in the validation data set. Performance characteristics of the criteria were also tested in patients with TAK and compared to those with GCA diagnosed between the ages of 50 and 60 years.

RESULTS

Generation of candidate classification items for the systemic vasculitides. The Steering Committee identified >1,000 candidate items for the DCVAS Case Report Form (see Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/art.42325).

DCVAS prospective observational study. Between January 2011 and December 2017, the DCVAS study recruited 6,991 participants from 136 sites in 32 countries. Information on the DCVAS sites, investigators, and study participants is listed in Supplementary Appendices 3, 4, and 5 (http://onlinelibrary.wiley.com/doi/10.1002/art.42325).

Expert review methodology to derive a gold standard–defined final set of cases of LVV. The LVV expert panel review process included 56 experts who reviewed vignettes derived from the Case Report Forms for 2,131 cases submitted with a diagnosis of LVV (1,608 [75.5% of Case Report Forms]), another type of vasculitis (118 [5.5% of Case Report Forms]), or a mimic of vasculitis (405 [19.0% of Case Report Forms]). Characteristics and the list of expert reviewers are shown in Supplementary Appendices 6 and 7 (http://onlinelibrary.wiley.com/doi/10.1002/art.42325). A sample vignette and the LVV expert panel review flow chart are shown in Supplementary Appendices 8 and 9 (http://onlinelibrary.wiley.com/doi/10.1002/art.42325). A total of 1,695 cases (80%) passed the main LVV process. An additional 373 cases of LVV and comparators, confirmed during a previous review process to derive the classification criteria for antineutrophil cytoplasmic antibody–associated vasculitis, were also included. In total, after both review processes, 2,068 cases were available for the stages 4 and 5 analyses.

The submitting physician diagnosis of GCA was confirmed in 913 of 1,137 cases (80.3%) after both expert panel reviews. The reasons for exclusion were diagnosis of GCA categorized as "uncertain" or "very uncertain" during panel review (n = 187) or change in diagnosis during panel review to another type of vasculitis (isolated aortitis, TAK, other vasculitides) (n = 11) or to a comparator disease (n = 26). An additional 29 patients who were not initially diagnosed as having GCA by the submitting physician were diagnosed as having GCA after panel review and DCVAS Steering Committee member adjudication. In total, 942 cases of confirmed GCA were available for analysis. To balance the number of cases of GCA with the number of available comparators, 756 cases of GCA were randomly selected for subsequent analysis.

Refinement of candidate items specifically for GCA. Only 7 of 942 patients with GCA (<1%) were diagnosed at age <50 years (see Supplementary Appendix 10 for the distribution of "age at diagnosis" in patients with LVV, and the similar

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distribution of "age at symptom onset," http://onlinelibrary.wiley.com/doi/10.1002/art.42325). Therefore, an age of ≥50 years at diagnosis was considered an absolute requirement to classify GCA. Cluster analyses of vascular imaging data identified bilateral axillary involvement and diffuse fluorodeoxyglucose uptake throughout the aorta on PET as specific imaging patterns for GCA (see Supplementary Appendices 11 and 12, http://onlinelibrary.wiley.com/doi/10.1002/art.42325). These imaging patterns were tested as potential classifiers.

Following a data-driven and expert consensus process, 72 items of the DCVAS Case Report Form were retained for regression analysis, including 32 demographic and clinical items, 14 laboratory items (including values of C-reactive protein [CRP] level and erythrocyte sedimentation rate [ESR], each divided into 5 categories), 14 imaging items (13 composite), 11 vascular examination items (5 composite, and upper extremity blood pressure divided into 6 categories), and 1 biopsy item (Supplementary Appendix 13, http://onlinelibrary.wiley.com/doi/10.1002/art.42325).

Derivation of the final classification criteria for GCA. A total of 1,505 patients were selected for analysis (756 GCA and 749 comparators), of which 1,054 (70%) were in the development data set (518 GCA and 536 comparators) and 451 (30%) in the validation data set (238 GCA and 213 comparators). Table 1 describes the demographic and clinical features of the patients with GCA and the comparators. The patients with GCA were recruited from Europe (n = 796), North America (n = 112), Oceania (n = 18), and Asia (n = 16). Clinical diagnoses assigned to patients in the comparator group are detailed in Supplementary Appendix 14 (http://onlinelibrary.wiley.com/doi/10.1002/art.42325).

Lasso regression of the previously selected 72 items yielded 27 independent predictor variables for GCA (Supplementary Appendix 15A, http://onlinelibrary.wiley.com/doi/10.1002/art.42325). Each predictor variable was then reviewed for inclusion by the DCVAS Steering Committee, based on their odds ratios and specificity to GCA, to ensure face validity. The variables "definitive vasculitis on TAB" and "halo sign on temporal artery ultrasound" were found to dominate the model as quite strong predictors of GCA (see Supplementary Appendix 16A for cluster plots showing almost a perfect overlap between the diagnosis of GCA and positive TAB or halo sign on temporal artery ultrasound, http://onlinelibrary.wiley.com/doi/10.1002/art.42325). Therefore, for the remaining variables to have discriminatory value, both of these items were removed from the model, combined into one composite item "vasculitis on TAB or halo sign on temporal artery ultrasound" and given a risk score of one point below the final threshold set to classify GCA to maintain face validity. The variables "jaw claudication" and "tongue claudication" were combined into 1 item, as were the variables "maximum ESR (>50 mm/hour)" and "maximum CRP (>10 mg/liter)." Although the variable "new persistent headache, occipital or cervical" showed important statistical significance, it decreased the overall specificity of the model when testing their final performance characteristics (patients versus comparators) and was, therefore, also removed. Weighting of the individual criterion

Table 1. Demographic and disease features of the patients with giant cell arteritis and the comparators*

	GCA (n = 756)	Comparators (n = 749)†	*P*
Age, mean ± SD years	72.2 ± 8.5	44.6 ± 18.0	<0.001
Female sex	511 (67.6)	447 (59.7)	0.001
Clinical features			
Morning stiffness, neck/torso	88 (11.6)	15 (2.0)	<0.001
Morning stiffness, shoulders/arms	174 (23.0)	23 (3.1)	<0.001
Sudden visual loss	102 (13.5)	29 (3.9)	<0.001
Jaw claudication	356 (47.1)	19 (2.5)	<0.001
Tongue claudication	21 (2.8)	1 (0.1)	<0.001
New persistent temporal headache	475 (62.8)	90 (12.0)	<0.001
Scalp tenderness	260 (34.4)	25 (3.3)	<0.001
Temporal artery abnormality on vascular examination‡	354 (46.8)	35 (4.7)	<0.001
Investigations			
Maximum ESR ≥50 mm/hour	558 (73.8)	291 (38.9)	<0.001
Maximum CRP ≥10 mg/liter	683 (90.3)	445 (59.4)	<0.001
Definitive vasculitis on temporal artery biopsy	335 (44.3)	1 (0.1)	<0.001
Halo sign on temporal artery ultrasound	211 (27.9)	1 (0.1)	<0.001
Bilateral axillary involvement on imaging§	57 (7.5)	12 (1.6)	<0.001
FDG-PET activity throughout aorta¶	52 (6.9)	9 (1.2)	<0.001

* Except where indicated otherwise, values are the number (%). ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; FDG-PET = ^{18}F-fluorodeoxyglucose–positron emission tomography.
† Diagnoses of comparators for the classification criteria for giant cell arteritis (GCA) included Takayasu arteritis (n = 251), Behçet's disease (n = 133), polyarteritis nodosa (n = 74), isolated aortitis (n = 16), primary central nervous system vasculitis (n = 16), large-vessel vasculitis (LVV) that could not be subtyped (n = 9), other diseases that mimic LVV (n = 250).
‡ Absent or diminished pulse, tenderness, or hard 'cord like' appearance.
§ Defined as damage (i.e., stenosis, occlusion, or aneurysm) on angiography (computed tomography, magnetic resonance, or catheter-based) or ultrasound, halo sign on ultrasound, or abnormal FDG uptake on PET.
¶ Descending thoracic and abdominal aorta.

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included in the model was based on logistic regression fitted to the remaining 9 selected predictors (Supplementary Appendix 17A, http://onlinelibrary.wiley.com/doi/10.1002/art.42325).

Validation of the final classification criteria for GCA. Using a cutoff of ≥6 in total risk score in the validation data set (see Supplementary Appendix 18A at https://onlinelibrary.wiley.com/doi/10.1002/art.42325 for different cutoff points), the sensitivity was 87.0% (95% confidence interval [95% CI] 82.0–91.0%) and specificity was 94.8% (95% CI 91.0–97.4%). The area under the curve for the model was 0.91 (95% CI 0.88–0.94) (Supplementary Appendix 19A, http://onlinelibrary.wiley.com/doi/10.1002/art.42325). The final 2022 ACR/EULAR classification criteria for GCA are presented in Figure 1 (for the slide presentation versions, see Supplementary Figure 1, http://onlinelibrary.wiley.com/doi/10.1002/art.42325).

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EULAR

CLASSIFICATION CRITERIA FOR **GIANT CELL ARTERITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify the patient as having giant cell arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

ABSOLUTE REQUIREMENT

Age ≥ 50 years at time of diagnosis	

ADDITIONAL CLINICAL CRITERIA

Morning stiffness in shoulders/neck	+2
Sudden visual loss	+3
Jaw or tongue claudication	+2
New temporal headache	+2
Scalp tenderness	+2
Abnormal examination of the temporal artery[1]	+2

LABORATORY, IMAGING, AND BIOPSY CRITERIA

Maximum ESR ≥ 50 mm/hour or maximum CRP ≥ 10 mg/liter[2]	+3
Positive temporal artery biopsy or halo sign on temporal artery ultrasound[3]	+5
Bilateral axillary involvement[4]	+2
FDG-PET activity throughout aorta[5]	+2

Sum the scores for 10 items, if present. A score of ≥ 6 points is needed for the classification of GIANT CELL ARTERITIS.

1. Examination of the temporal artery showing absent or diminished pulse, tenderness, or hard 'cord-like' appearance.
2. Maximum erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) values prior to initiation of treatment for vasculitis.
3. Presence of either definitive vasculitis on temporal artery biopsy or halo sign on temporal artery ultrasound. There are no specific histopathologic criteria to define definitive vasculitis on temporal artery biopsy. Presence of giant cells, mononuclear leukocyte infiltration, and fragmentation of the internal elastic lamina were independently associated with histopathologic interpretation of definite vasculitis in the DCVAS cohort [24]. Halo sign is defined by the presence of an homogenous, hypoechoic wall thickening on ultrasound [25].
4. Bilateral axillary involvement is defined as luminal damage (stenosis, occlusion, or aneurysm) on angiography (computed tomography, magnetic resonance, or catheter-based) or ultrasound, halo sign on ultrasound, or fluorodeoxyglucose uptake on positron emission tomography.
5. Abnormal fluorodeoxyglucose (FDG) uptake in the arterial wall (e.g., greater than liver uptake by visual inspection) throughout the descending thoracic and abdominal aorta on positron emission tomography (PET).

Figure 1. The final 2022 American College of Rheumatology/EULAR Classification Criteria for Giant Cell Arteritis.

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Table 2. Performance characteristics of the 2022 ACR/EULAR classification criteria for giant cell arteritis*

Patient subset	Total no. patients (no. GCA patients)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Development data set	1,054 (518)	84.8 (81.4–87.7)	95.0 (92.8–96.7)	0.90 (0.88–0.92)
Validation data set	451 (238)	87.0 (82.0–91.0)	94.8 (91.0–97.4)	0.91 (0.88–0.94)
Biopsy-proven GCA†	1,104 (355)	100.0 (99.0–100.0)	94.9 (93.1–96.4)	0.97 (0.97–0.98)
Large-vessel GCA‡	873 (124)	55.7 (46.5–64.6)	94.9 (93.1–96.4)	0.75 (0.71–0.80)

* Performance characteristics were tested in the subsets using the combined development and validation data sets to maximize sample size. ACR = American College of Rheumatology; GCA = giant cell arteritis; 95% CI = 95% confidence interval; AUC = area under the curve.
† Definite vasculitis on temporal artery biopsy (TAB).
‡ Involvement of the aorta or its branch arteries on imaging, without vasculitis on TAB.

The performance characteristics of the criteria in different subsets of patients with GCA are shown in Table 2 and Supplementary Appendix 20A (https://onlinelibrary.wiley.com/doi/10.1002/art.42325). Biopsy-proven GCA showed a sensitivity of 100% (95% CI 99.0–100.0%) and a specificity of 94.9% (95% CI 93.1–96.4%), and large-vessel GCA showed a sensitivity of 55.7% (95% CI 46.5–64.6%) and a specificity of 94.9% (93.1–96.4%). Sensitivity of the criteria in North America was 77.8% (95% CI 67.8–85.9%) and in Europe was 87.2% (95% CI 84.4–89.7%). Specificity in North America was 95.6% (95% CI 90.6–98.4%) and in Europe was 88.8% (95% CI 84.9–92.0%).

When the 1990 ACR classification criteria for GCA were applied to the DCVAS validation data set, the criteria performed poorly due to low sensitivity (80.3% [95% CI 74.6–85.1%]) but retained good specificity (92.5% [95% CI 88.1–95.7%]). In particular, the 1990 ACR criteria had poor sensitivity for patients with large-vessel GCA (37.1% [95% CI 28.6–46.2%]).

Age restrictions are absolute requirements for the 2022 ACR/EULAR classification criteria for GCA (≥50 years at diagnosis) and TAK (≤60 years at diagnosis). However, of the 70 patients with GCA diagnosed between the ages of 50 and 60 years, 44 (62.9%) met the new GCA classification criteria, 9 (12.9%) met the new TAK classification criteria, and only 2 (2.9%) met both the new GCA and TAK classification criteria (Supplementary Appendix 21, http://onlinelibrary.wiley.com/doi/10.1002/art.42325).

DISCUSSION

Presented here are the final 2022 ACR/EULAR GCA classification criteria. A 6-stage approach was used, underpinned by data from the multinational, prospective DCVAS study and informed by expert review and consensus at each stage. The comparator group for developing and validating the criteria were other vasculitides and conditions that mimic GCA, where discrimination from GCA is difficult but important. In the validation set, the new criteria had a sensitivity of 87.0% (95% CI 82.0–91.0%) and a specificity of 94.8% (95% CI 91.0–97.4%). These are the official final values that should be quoted when referring to the criteria. The sensitivity and specificity values calculated in the development set were very similar, providing reassurance that the statistical methods avoided overfitting of models. The new criteria incorporate modern imaging techniques and have excellent specificity and sensitivity within a large, international cohort of patients with GCA. The criteria were designed to have face and content validity for use in clinical trials and other research studies.

These criteria are validated and intended for the purpose of *classification* of vasculitis and are not appropriate for use to establish a *diagnosis* of vasculitis. The aim of the classification criteria is to differentiate cases of GCA from similar types of vasculitis in research settings (21). *Therefore, the criteria should only be applied when a diagnosis of large- or medium-vessel vasculitis has been made and all potential "vasculitis mimics" have been excluded*. The exclusion of mimics is a key aspect of many classification criteria including those for Sjögren's syndrome (22) and rheumatoid arthritis (16). The 1990 ACR classification criteria for vasculitis perform poorly when used for diagnosis (i.e., when used to differentiate between cases of vasculitis versus mimics without vasculitis) (23), and it is expected that the 2022 criteria would also perform poorly if used inappropriately as diagnostic criteria in people for whom alternative diagnoses, such as infection or other non-vasculitis inflammatory diseases, are still being considered.

The 2022 ACR/EULAR GCA classification criteria are the result of an incredibly large worldwide effort, in which an extensive set of data was collected from >1,000 patients with the submitted diagnosis of GCA. These criteria reflect current clinical practice, integrating different investigative methods (e.g., TAB, ultrasound, angiography, PET) from various countries and medical specialties. Real cases of GCA and comparators were reviewed by a wide range of experts in vasculitis to establish an unbiased diagnostic reference to derive the criteria. Advanced statistical methods including lasso logistic regression and cluster analyses were applied, which facilitated testing for different covariates of interest, namely specific patterns of vasculitic involvement in imaging. Modern classification techniques with weighted criterion with threshold scores were used, allowing for more discriminatory items to factor more heavily in disease classification.

When compared to the original 1990 ACR classification criteria for GCA, the 2022 ACR/EULAR GCA classification criteria

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demonstrated greater sensitivity while maintaining similar specificity to the 1990 criteria. In particular, the new criteria were able to correctly classify more patients with the large-vessel GCA subtype, in whom the sensitivity of the 1990 ACR criteria was only 37.1%. Unlike the 1990 ACR criteria, an age of ≥50 years at diagnosis is a mandatory requirement to classify GCA in the 2022 ACR/EULAR criteria. This age threshold included >99% of patients with the reference diagnosis of GCA. The new criteria maintain good discriminative ability for patients diagnosed between the ages of 50 and 60 years, the interval where the absolute age requirements for the 2022 ACR/EULAR criteria for GCA and for TAK can overlap.

A potential limitation of these criteria was the nonstandardized acquisition of clinical and imaging data among patients with LVV and comparators (e.g., not all patients underwent vascular examination of the temporal arteries, PET was not available in many centers treating patients with LVV, and TAB and/or ultrasound was not performed in all patients with suspected GCA, etc.). However, this reflects existing differences in clinical practice, and the 11 items included in the criteria allow for a feasible evaluation of patients in any clinical setting. These criteria also provide flexibility for classifying a patient, regardless of the diagnostic assessment strategy employed by physicians. Definite vasculitis on TAB was defined by the submitting physician and did not undergo central review; ~20% of cases did not have specific histopathologic findings but were reported as "definitive vasculitis on TAB" alone. Most patients were recruited from Europe and North America, with fewer patients from Asia and Oceania. The performance characteristics of the criteria should be further tested in other populations that were underrepresented in the DCVAS cohort and may have different clinical presentations of GCA.

The 2022 ACR/EULAR classification criteria for GCA are the product of a rigorous methodologic process that utilized an extensive data set generated by the work of a remarkable international group of collaborators. These criteria have been endorsed by the ACR and EULAR and are now ready for use in clinical research.

ACKNOWLEDGMENTS

We acknowledge the patients and clinicians who provided data to the DCVAS project.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Merkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Arthritis & Rheumatology
Vol. 74, No. 3, March 2022, pp 393–399
DOI 10.1002/art.41986
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Empowering Rheumatology Professionals

2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Granulomatosis With Polyangiitis

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European Alliance of Associations for Rheumatology (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

The ACR is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.

Objective. To develop and validate revised classification criteria for granulomatosis with polyangiitis (GPA).

Methods. Patients with vasculitis or comparator diseases were recruited into an international cohort. The study proceeded in 5 phases: 1) identification of candidate criteria items using consensus methodology, 2) prospective collection of candidate items present at the time of diagnosis, 3) data-driven reduction of the number of candidate items, 4) expert panel review of cases to define the reference diagnosis, and 5) derivation of a points-based risk score for disease classification in a development set using least absolute shrinkage and selection operator logistic regression, with subsequent validation of performance characteristics in an independent set of cases and comparators.

Results. The development set for GPA consisted of 578 cases of GPA and 652 comparators. The validation set consisted of an additional 146 cases of GPA and 161 comparators. From 91 candidate items, regression analysis identified 26 items for GPA, 10 of which were retained. The final criteria and their weights were as follows: bloody nasal discharge, nasal crusting, or sino-nasal congestion (+3); cartilaginous involvement (+2); conductive or sensorineural hearing loss (+1); cytoplasmic antineutrophil cytoplasmic antibody (ANCA) or anti–proteinase 3 ANCA positivity (+5); pulmonary nodules, mass, or cavitation on chest imaging (+2); granuloma or giant cells on biopsy (+2); inflammation or consolidation of the nasal/paranasal sinuses on imaging (+1); pauci-immune glomerulonephritis (+1); perinuclear ANCA or antimyeloperoxidase ANCA positivity (−1); and eosinophil count ≥1 × 10^9/liter (−4). After excluding mimics of vasculitis, a patient with a diagnosis of small- or medium-vessel vasculitis could be classified as having GPA if the cumulative score was ≥5 points. When these criteria were tested in the validation data set, the sensitivity was 93% (95% confidence interval [95% CI] 87–96%) and the specificity was 94% (95% CI 89–97%).

Conclusion. The 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for GPA demonstrate strong performance characteristics and are validated for use in research.

This article is published simultaneously in the March 2022 issue of *Annals of the Rheumatic Diseases*.

The Diagnostic and Classification Criteria in Vasculitis (DCVAS) study, of which the development of these classification criteria was a part, was funded by grants from the American College of Rheumatology (ACR), the European Alliance of Associations for Rheumatology (EULAR), the Vasculitis Foundation, and the University of Pennsylvania Vasculitis Center.

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INTRODUCTION

The antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV) are multisystem disorders involving inflammation of the small blood vessels and include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (1). GPA is characterized by necrotizing granulomatous inflammation involving the ears, nose, and upper and lower respiratory tracts, and necrotizing vasculitis affecting predominantly small- to medium-sized vessels, often including necrotizing glomerulonephritis (1).

Unlike diagnostic criteria, the purpose of classification criteria is to ensure that a homogeneous population is selected for inclusion in clinical trials and other research studies of GPA. In 1990, the American College of Rheumatology (ACR) published criteria for the classification of GPA (then named Wegener's granulomatosis) (2–4). The 1990 criteria were effective and widely accepted, facilitating coordinated approaches to international randomized controlled trials (5,6). In 2011 it was proposed to change the name "Wegener's granulomatosis" to "granulomatosis with polyangiitis" with subsequent wide adoption of the new terminology (7–9). The 1994 and 2012 publications of the international Chapel Hill Consensus Conference (CHCC) nomenclature for vasculitis clarified and standardized the nomenclature of the systemic vasculitides (1,10). The CHCC is a nomenclature system based on expert consensus rather than a classification system (1).

There are several important reasons for the development of revised classification criteria for the vasculitides, including a decline in the sensitivity of the 1990 ACR classification criteria, particularly for AAV (11); a consensus that any such criteria must now incorporate testing for ANCA; increased and widespread use, since 1990, of cross-sectional diagnostic imaging tools, including magnetic resonance imaging and computed tomography (12,13); and the introduction and adoption of the classification of patients with MPA, a term not in use in the 1990 ACR classification criteria.

There have been methodologic advances in the derivation of classification criteria, moving from the "number of criteria" rule, as used in the ACR 1990 criteria (3), toward weighted criteria with threshold scores, as demonstrated in the 2010 classification criteria for rheumatoid arthritis (14). Weighted criteria improve measurement properties of classification criteria because certain items within a criteria list may be more discriminative. The previous 1990 criteria for vasculitis collected retrospective data from patient files, without specification of which items were relevant at the time of diagnosis compared to those that were important later in the disease process. Criteria based on prospectively collected data sets from newly diagnosed patients should have higher face validity as inclusion criteria for future clinical trials of early-stage disease. This article outlines the development and validation of the revised ACR/European Alliance of Associations for Rheumatology (EULAR)–endorsed classification criteria for GPA.

METHODS

A detailed and complete description of the methods involved in the development and validation of the classification criteria for GPA is provided in Supplementary Appendix 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract. Briefly, an international Steering Committee comprising clinician investigators with expertise in vasculitis, statisticians, and data managers was established to oversee the overall Diagnostic and Classification Criteria in Vasculitis (DCVAS) project (15). The Steering Committee established a 5-stage plan using data-driven and consensus methodology to develop the criteria for each of 6 forms of vasculitis.

Stage 1: generation of candidate classification items for the systemic vasculitides. Candidate classification items were generated by expert opinion and reviewed by a group of vasculitis experts across a range of specialties using a nominal group technique.

Stage 2: DCVAS prospective observational study. A prospective, international, multisite observational study was conducted (see Appendix A for study investigators and sites). Ethical approval was obtained from national and local ethics committees. Consecutive patients representing the full spectrum of disease were recruited from academic and community practices. Patients were included if they were 18 years or older and had a diagnosis of vasculitis or a condition that mimics vasculitis. Patients with AAV could only be enrolled within 2 years of diagnosis. Only data present at diagnosis were recorded.

Stage 3: refinement of candidate items specifically for AAV. The Steering Committee conducted a data-driven process to reduce the number of candidate items of relevance to cases and comparators for AAV. Items were selected for exclusion if they had a prevalence of <5% within the data set and/or they were not clinically relevant for classification criteria (e.g., related to infection, malignancy, or demographic characteristics). Low-frequency items of clinical importance could be combined, when appropriate.

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Submitted for publication February 28, 2020; accepted in revised form September 21, 2021.

Stage 4: expert review to derive a gold standard–defined set of cases of AAV. Experts in vasculitis from a wide range of geographic locations and specialties reviewed all submitted cases of vasculitis and a random selection of mimics of vasculitis. Each reviewer was asked to review ~50 submitted cases to confirm the diagnosis and to specify the certainty of their diagnosis as follows: very certain, moderately certain, uncertain, or very uncertain. Only cases agreed upon with at least moderate certainty were retained for further analysis.

Stage 5: derivation and validation of the final classification criteria for GPA. The DCVAS AAV data set was randomly split into development (80%) and validation (20%) sets. Comparisons were performed between cases of GPA confirmed by expert review and a comparator group randomly selected from the DCVAS cohort in the following proportions: another type of AAV (including MPA and EGPA), 64%; another form of small-vessel vasculitis (e.g., cryoglobulinemic vasculitis) or medium-vessel vasculitis (e.g., polyarteritis nodosa), 36%. Least absolute shrinkage and selection operator (lasso) logistic regression was used to identify items from the data set and create a parsimonious model including only the most important items. The final items in the model were formulated into a clinical risk-scoring tool with each factor assigned a weight based on its respective regression coefficient. A threshold that best balanced sensitivity and specificity was identified for classification.

In sensitivity analyses, the final classification criteria were applied to an unselected population of cases and comparators from the DCVAS data set based on the submitting physician diagnosis. Comparison was also made between the measurement properties of the new classification criteria for GPA and the 1990 ACR classification criteria for GPA using pooled data from the development and validation sets.

RESULTS

Generation of candidate classification items for the systemic vasculitides. The Steering Committee identified >1,000 candidate items for the DCVAS case report form (see Supplementary Appendix 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract).

DCVAS prospective observational study. Between January 2011 and December 2017, the DCVAS study recruited 6,991 participants from 136 sites in 32 countries. Information on the DCVAS sites, investigators, and study participants is listed in Supplementary Appendices 3, 4, and 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract.

Refinement of candidate items specifically for AAV. Following a data-driven and expert consensus process, 91 items from the DCVAS case report form were retained for regression analysis, including 45 clinical (14 composite), 18 laboratory (2 composite), 12 imaging (all composite), and 16 biopsy (1 composite) items. Some clinical items were removed in favor of similar but more specific pathophysiologic descriptors. Supplementary Appendix 6, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract, lists the final candidate items used in the derivation of the classification criteria for GPA, MPA, and EGPA.

Expert review to derive a gold standard–defined final set of cases of AAV. Fifty-five independent experts reviewed vignettes derived from the case report forms for 2,871 cases submitted with a diagnosis of either small-vessel vasculitis

Table 1. Demographic and disease features of cases of GPA and comparators*

	GPA (n = 724)	Comparators (n = 813)†	*P*
Age, mean ± SD years	53.6 ± 16.2	56.4 ± 17.1	0.001
Sex, no. (%) female	340 (47.0)	424 (52.2)	0.048
Maximum serum creatinine, mean			0.077
μmoles/liter	168.3	185.2	
mg/dl	1.9	2.1	
cANCA positive, no. (%)	531 (73.3)	40 (4.9)	<0.001
pANCA positive, no. (%)	71 (9.8)	342 (42.1)	<0.001
Anti–PR3-ANCA positive, no. (%)	595 (82.2)	21 (2.6)	<0.001
Anti–MPO-ANCA positive, no. (%)	59 (8.1)	399 (49.1)	<0.001
Maximum eosinophil count ≥1 × 10^9/liter, no. (%)	196 (27)	366 (45)	<0.001

* cANCA = cytoplasmic antineutrophil cytoplasmic antibody; pANCA = perinuclear ANCA; anti–PR3-ANCA = anti–proteinase 3–ANCA; anti–MPO-ANCA = anti–myeloperoxidase-ANCA.
† Diagnoses of comparators for the classification criteria for granulomatosis with polyangiitis (GPA) included microscopic polyangiitis (n = 291), eosinophilic granulomatosis with polyangiitis (n = 226), polyarteritis nodosa (n = 51), non–ANCA-associated small-vessel vasculitis that could not be subtyped (n = 51), Behçet's disease (n = 50), IgA vasculitis (n = 50), cryoglobulinemic vasculitis (n = 34), ANCA-associated vasculitis that could not be subtyped (n = 25), primary central nervous system vasculitis (n = 19), and anti–glomerular basement membrane disease (n = 16).

(90% of case report forms) or another type of vasculitis or a mimic of vasculitis (10% of case report forms). The characteristics of the expert reviewers are shown in Supplementary Appendix 7, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract. A flow chart showing the results of the expert review process is shown in Supplementary Appendix 8, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract. A total of 2,072 cases (72%) passed the process and were designated as cases of vasculitis; these cases were used for the stage 5 analyses.

After expert review, 724 of 843 cases retained a reference diagnosis of GPA. There were 813 comparators randomly selected for analysis. Table 1 shows the demographic and disease features of the 1,537 cases included in this analysis (724 patients with GPA and 813 comparators), of which 1,230 (80%, 578 patients with GPA and 652 comparators) were in the development set, and 307 (20%, 146 patients with GPA and 161 comparators) were in the validation set.

Derivation and validation of the final classification criteria for GPA. Lasso logistic regression analysis using all 91 items resulted in a model of 26 independent items (see Supplementary Appendix 9B, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract). The variables "positive test for cytoplasmic ANCA (cANCA)" and "positive test for anti–proteinase 3 (anti-PR3)

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

CLASSIFICATION CRITERIA FOR **GRANULOMATOSIS WITH POLYANGIITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify a patient as having granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

CLINICAL CRITERIA

Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage, or septal defect / perforation	+3
Cartilaginous involvement (inflammation of ear or nose cartilage, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	+2
Conductive or sensorineural hearing loss	+1

LABORATORY, IMAGING, AND BIOPSY CRITERIA

Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	+5
Pulmonary nodules, mass, or cavitation on chest imaging	+2
Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	+1
Pauci-immune glomerulonephritis on biopsy	+1
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies	-1
Blood eosinophil count ≥ 1 x10^9/liter	-4

Sum the scores for 10 items, if present. A score of ≥ 5 is needed for classification of GRANULOMATOSIS WITH POLYANGIITIS.

Figure 1. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis.

antibody" and the variables "positive test for perinuclear ANCA (pANCA)" and "positive test for antimyeloperoxidase (anti-MPO) antibody" were strongly colinear and were combined within the model as "positive test for cANCA or positive test for anti-PR3 antibody" and "positive test for pANCA or positive test for anti-MPO antibody," respectively. Each item was scrutinized for inclusion based on statistical significance, clinical relevance, and specificity to GPA, resulting in 10 final items. Weighting of an individual criterion was based on logistic regression fitted to the 10 selected items (see Supplementary Appendix 10B, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract).

Model performance. Use of a cutoff of ≥5 for total risk score (see Supplementary Appendix 11B, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract, for different cut points) yielded a sensitivity of 92.5% (95% confidence interval [95% CI] 86.9–96.2%) and a specificity of 93.8% (95% CI 88.9–97.0%) in the validation set. The area under the curve (AUC) for the model was 0.98 (95% CI 0.98–0.99) in the development set and 0.99 (95% CI 0.98–1.00) in the validation set (Supplementary Appendix 12B, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract). The final classification criteria for GPA are shown in Figure 1 (for the slide presentation version, see Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract).

Sensitivity analyses. The classification criteria for GPA were applied to 2,511 patients randomly selected from the DCVAS database using the original physician-submitted diagnosis (n = 483 GPA and 2,028 comparators). Use of the same cut point of ≥5 points for the classification of GPA yielded a similar specificity of 94.6% but a lower sensitivity of 83.8%. This upheld the a priori hypothesis that specificity would remain unchanged but sensitivity would be reduced in a population with fewer clear-cut diagnoses of GPA (i.e., cases that did not pass expert review).

When the 1990 ACR classification criteria for GPA were applied to the DCVAS data set, the criteria performed poorly due to low sensitivity (69.3%) and moderate specificity (75.8%), with an AUC of 0.73 (95% CI 0.70–0.75).

DISCUSSION

Presented here are the final 2022 ACR/EULAR GPA classification criteria. A 5-stage approach has been used, underpinned by data from the multinational prospective DCVAS study and informed by expert review and consensus at each stage. The comparator group for developing and validating the criteria were other forms of AAV and other small- and medium-vessel vasculitides, the clinical entities where discrimination from GPA is difficult, but important. The new criteria for GPA have excellent sensitivity and specificity and incorporate ANCA testing and modern imaging techniques. The criteria were designed to have face and content validity for use in clinical trials and other research studies.

These criteria are validated and intended for the purpose of *classification* of vasculitis and are not appropriate for use in establishing a *diagnosis* of vasculitis. The aim of the classification criteria is to differentiate cases of GPA from similar types of vasculitis in research settings. Therefore, the criteria should only be applied when a diagnosis of small- or medium-vessel vasculitis has been made and all potential "vasculitis mimics" have been excluded. The exclusion of mimics is a key aspect of many classification criteria, including those for Sjögren's syndrome (16) and rheumatoid arthritis (14). The 1990 ACR classification criteria for vasculitis perform poorly when used for diagnosis (i.e., when used to differentiate between cases of vasculitis versus mimics without vasculitis) (17), and it is expected that the 2022 criteria would also perform poorly if used inappropriately as diagnostic criteria in people in whom alternative diagnoses, such as infection or other non-vasculitis inflammatory diseases, are still being considered. The relatively low weight assigned to glomerulonephritis in these classification criteria highlights the distinction between classification and diagnostic criteria. While detection of kidney disease is important to diagnose GPA, glomerulonephritis is common among patients with either GPA or MPA and thus does not function as a strong classifier between these conditions.

These criteria differ from the previous 1990 ACR criteria in that they have been developed using cases presenting prospectively at the start of their disease process. This approach is different from the methods used to generate the 1990 ACR criteria, in which prevalent case records were utilized, potentially including items related to irreversible damage accrued over time. Inclusion of newly diagnosed cases in these criteria should improve their accuracy within the context of early intervention trials as well as refractory disease. The comparators used for these new criteria are also more appropriate and are closer mimics of GPA; for example, comparators with predominantly small-vessel vasculitis rather than predominantly giant cell arteritis were included. The new criteria perform better than previous criteria within this data set (11). ANCA is a major discriminator within these criteria, although patients can be classified as having GPA without having a positive test result for ANCA if they have a sufficient number of other features. These new criteria were validated in an independent data set and are weighted with threshold scores (14,16) to maximize predictive ability.

There are some study limitations to consider. Although this was the largest international study ever conducted in vasculitis, most patients were recruited from Europe, Asia, and North America. The performance characteristics of the criteria should be further tested in African and South American populations, which may have different clinical presentations of vasculitis. These

criteria were developed using data collected from adult patients with vasculitis. Although the clinical characteristics of GPA and the other vasculitides which these criteria were tested against are not known to differ substantially between adults and children, these criteria should be applied to children with some caution. The scope of the criteria is intentionally narrow and applies only to patients who have been diagnosed as having vasculitis. Diagnostic criteria are not specified. The criteria are intended to identify homogeneous populations of disease and, therefore, may not be appropriate for studies focused on the full spectrum of clinical heterogeneity in these conditions. To maximize relevance and face validity of the new criteria, study sites and expert reviewers were recruited from a broad range of countries and different medical specialties. Nonetheless, the majority of patients were recruited from academic rheumatology or nephrology units, which could have introduced referral bias.

A key strength of this study is the use of an independent expert review process to confirm cases of GPA and comparators to avoid the circularity of using predefined criteria to define the gold standard. Approximately one-quarter of cases were excluded via this process, due to either a lack of consensus on exact diagnosis or insufficient data available to make the diagnosis. A limitation of this approach, however, could be the exclusion of true, but less clearcut, cases submitted by the original physicians. It is important that cases are classified accurately for inclusion in clinical trials; therefore, some loss of sensitivity may be appropriate. Importantly, this study also demonstrated that applying the new criteria for GPA to the whole unselected DCVAS data set resulted in a reduction in sensitivity while maintaining specificity. Thus, the criteria should also be useful in a more generalized, "real-world" population.

The 2022 ACR/EULAR classification criteria for GPA are the product of a rigorous methodologic process that utilized an extensive data set generated by the work of a remarkable international group of collaborators. These criteria have been endorsed by the ACR and EULAR and are now ready for use to differentiate one type of vasculitis from another to define populations in research studies.

ACKNOWLEDGMENTS

We acknowledge the patients and clinicians who provided data to the DCVAS project.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Merkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Arthritis & Rheumatology
Vol. 74, No. 4, April 2022, pp 586–596
DOI 10.1002/art.42041
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American College of Rheumatology
Empowering Rheumatology Professionals

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease

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Objective. To provide evidence-based recommendations and expert guidance for the management of Kawasaki disease (KD), focusing on clinical scenarios more commonly addressed by rheumatologists.

Methods. Sixteen clinical questions regarding diagnostic testing, treatment, and management of KD were developed in the Patient/Population, Intervention, Comparison, and Outcomes (PICO) question format. Systematic literature reviews were conducted for each PICO question. We used the Grading of Recommendations, Assessment, Development and Evaluation method to assess the quality of evidence and formulate recommendations. Each recommendation required consensus from at least 70% of the Voting Panel.

Results. We present 1 good practice statement, 11 recommendations, and 1 ungraded position statement to guide the management of KD and clinical scenarios of suspected KD. These recommendations for KD are focused on situations in which input from rheumatologists may be requested by other managing specialists, such as in cases of treatment-refractory, severe, or complicated KD. The good practice statement affirms that all patients with KD should receive initial treatment with intravenous immunoglobulin (IVIG). In addition, we developed 7 strong and 4 conditional recommendations for the management of KD or suspected KD. Strong recommendations include prompt treatment of incomplete KD, treatment with aspirin, and obtaining an echocardiogram in the setting of unexplained macrophage activation syndrome or shock. Conditional recommendations include use of IVIG with other adjuvant agents for patients with KD and high-risk features of IVIG resistance and/or coronary artery aneurysms. These recommendations endorse minimizing risk to the patient by using established therapy promptly at disease onset and identifying situations in which adjunctive therapy may be warranted.

Conclusion. These recommendations provide guidance regarding diagnostic strategies, use of pharmacologic agents, and use of echocardiography in patients with suspected or confirmed KD.

INTRODUCTION

Kawasaki disease (KD) is a medium vessel vasculitis as presented in the Chapel Hill Consensus Conference nomenclature system (1). It is 1 of 2 primary common vasculitis syndromes that predominantly affect children (the other being IgA vasculitis [Henoch-Schönlein]). KD is seen with relative frequency in young children, at an incidence rate of 25–50 cases per 100,000 persons per year in the US, similar to that of type 1 diabetes (2,3). It typically presents in children <5 years of age as an acute, self-limited febrile disease and is characterized by a combination of several characteristic clinical signs, which include polymorphic rash, nonpurulent conjunctival injection, oropharyngeal and lip mucositis, tongue papillitis, erythema and edema of the hands and feet, as well as unilateral cervical lymphadenopathy.

From a histopathologic perspective, KD is characterized by aggressive neutrophil-mediated panmural vascular necrosis without granuloma formation, followed by intimal hyperplasia and subacute lymphocytic inflammation in advanced disease. It primarily affects the coronary arteries but can also affect medium-caliber arteries throughout the body (4). Therefore, it shares some features with polyarteritis nodosa, and prior to the recognition of KD as a distinct entity, infants with fatal fulminant forms of KD were considered to have "infantile polyarteritis nodosa" (5).

When treated appropriately, KD is associated with a low mortality rate (~0.08% case fatality rate in the largest reported series) (6). However, in the developed world, it is the most common cause of acquired cardiac disease in childhood, with 25% of untreated patients and 5% of treated patients developing coronary artery aneurysms. Among infants <6 months of age, the risk of a coronary artery aneurysm is 50%, even in KD patients who received treatment with intravenous immunoglobulin (IVIG) within the first 10 days of illness (7).

Given increasing options available to treat systemic vasculitis, the American College of Rheumatology (ACR) and Vasculitis Foundation supported the development of guidelines for the management of large, medium, and small vessel vasculitis. This guideline presents evidence-based recommendations for the diagnostic testing, treatment, and management of KD. Recognizing the comprehensive guidelines developed by the American Heart Association (AHA) for the management of KD (3), the guideline focuses on clinical management questions that are generally posed to rheumatologists, such as the use of adjunctive therapies for initial treatment of severe disease and treatment approaches for refractory disease. Although this guideline may inform an international audience, these recommendations were developed considering experience with and availability of treatment and diagnostic options in the US.

METHODS

This guideline followed the ACR guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and develop recommendations (8,9). ACR policy guided the management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis). Supplementary Appendix 1 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42041/abstract) presents a detailed description of the methods.

Sixteen clinical questions addressing the diagnostic testing, treatment, and management of KD were developed by the Core Team, initial Voting Panel, and Expert Panel in the Patient/Population, Intervention, Comparison, and Outcomes (PICO) format. The Literature Review Team undertook systematic literature reviews

This article is published simultaneously in *Arthritis Care & Research*.

Supported by the American College of Rheumatology and the Vasculitis Foundation.

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.42041&file=art42041-sup-0001-Disclosureform.pdf.

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Submitted for publication July 20, 2021; accepted in revised form December 2, 2021.

for prespecified PICO questions. The Expert Panel, including rheumatologists and a pediatric cardiologist, provided expert knowledge to inform discussion of the PICO questions and findings of the literature review. This study did not involve human subjects, and therefore, approval from Human Studies Committees was not required.

The initial Voting Panel comprised 9 adult rheumatologists (SAC, AMA, DLC, PCG, PAM, RLR, PS, JHS, AW), 5 pediatric rheumatologists (LFI, SK, SS, MFI, RPS), and 2 patients (KAF, OIV). They reviewed the Literature Review Team's evidence summaries and formulated and voted on an initial set of recommendations. To incorporate broader expertise from the pediatric community and validate the results from the initial Voting Panel, a second Voting Panel was established and comprised 8 pediatric rheumatologists new to the Voting Panel (MG, KA, BAB, KH, SKL, MBS, HVM, CY-T), 4 pediatric rheumatologists who participated in both Voting Panels (LFI, SK, SS, RPS), a pediatric infectious disease physician with extensive expertise in KD (AHT), and a pediatric cardiologist with extensive expertise in KD (KF). The second Voting Panel also reviewed the Literature Review Team's findings and independently formulated and voted on recommendations. Members of the second Voting Panel who were not on the initial Voting Panel were not provided with the recommendations formulated by the initial Voting Panel prior to the second panel's voting. Each recommendation required consensus from at least 70% of the Voting Panel.

How to interpret the recommendations

A *strong* recommendation is typically supported by moderate- to high-quality evidence (e.g., multiple randomized controlled trials). For a strong recommendation, the recommended course of action would apply to all or almost all patients. Only a small proportion of clinicians/patients would not want to follow the recommendation. For example, an intervention may be strongly recommended if it is considered low-cost, without harms, and the consequence of not performing the intervention may be catastrophic. An intervention may be strongly recommended against if there is high certainty that the intervention will lead to more harm than the comparison with very low or low certainty about its benefit (10).

A *conditional* recommendation is generally supported by lower-quality evidence or a close balance between desirable and undesirable outcomes. For a conditional recommendation, the recommended course of action would apply to the majority of patients, but the alternative is a reasonable consideration. Conditional recommendations always warrant a shared decision-making approach. We specify conditions under which the alternative may be considered.

In one instance, the committee found that the evidence for a particular PICO question did not support a graded recommendation, and the Voting Panel did not favor one intervention over another. However, the Voting Panel believed the PICO question addressed a commonly encountered clinical question, and thus felt that providing guidance for this question was warranted. For this situation, we present an "ungraded position statement" which reflects general views of the Voting Panel.

In this evidence-based guideline, we explicitly used the best evidence available and present it in a transparent manner for the clinician reader/user (10). In some instances, this includes randomized trials in which the interventions under consideration are directly compared. The GRADE system rates evidence that

Table 1. Definitions of selected terms used in the recommendations/ungraded position statements for KD*

Term	Definition
Disease states	
KD	Fever lasting at least 5 days without any other explanation with at least 4 of the 5 following principal clinical findings: 1) bilateral bulbar conjunctival injection without exudate, 2) erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa, 3) erythema and edema of the hands or feet (acute phase), and/or periungual desquamation (subacute phase), 4) maculopapular, diffuse erythroderma, or erythema multiforme–like rash, or 5) cervical lymphadenopathy (at least 1 lymph node >1.5 cm in diameter), usually unilaterally. The diagnosis may be made with only 4 days of fever if ≥4 principal clinical findings are present.
Incomplete KD	Prolonged unexplained fever in an infant or child with <4 of the principal clinical findings of KD (see above), and compatible laboratory markers (elevated ESR/CRP level, elevated transaminase levels, UA with leukocyte esterase–negative WBCs) or echocardiographic findings (coronary artery dilatation), defined according to the algorithm in references 3 and 31
Acute KD	Initial febrile phase of KD
Medications	
IVIG	Single dose of 2 gm/kg (no defined maximum dose, but the reasonable maximum range is 100–140 gm)
Nonglucocorticoid immunomodulatory therapy	Anakinra, cyclosporine, or infliximab
Glucocorticoids	Prednisone 2 mg/kg/day (maximum dose 60 mg/day) tapered over 15 days, or equivalent
Aspirin	High dose: 80–100 mg/kg/day; moderate dose: 30–50 mg/kg/day; low dose: 3–5 mg/kg/day

* KD = Kawasaki disease; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; UA = uric acid; WBCs = white blood cells; IVIG = intravenous immunoglobulin.

comes exclusively from the collective experience of the Voting Panel and Patient Panel members as "very low–quality" evidence.

For each recommendation, details regarding the PICO questions and the GRADE evidence tables can be found in Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.42041/abstract).

RESULTS

For the evidence report, the Literature Review Team summarized 275 articles to address 16 PICO questions for KD. Details regarding the methods utilized for the literature review are provided in Supplementary Appendix 1 (http://onlinelibrary.wiley.com/doi/10.1002/art.42041/abstract). Both the initial and second Voting Panel utilized the evidence report to formulate their recommendations. The recommendations formulated by the second Voting Panel were consistent with those of the initial Voting Panel. Clinical considerations for the recommendations were further expanded by the second Voting Panel, and thus the recommendations of the second Voting Panel are presented here.

Table 1 presents definitions of selected terms used in the recommendations, and Table 2 presents the recommendations with their supporting PICO questions and level of evidence. Figure 1 shows a schematic highlighting the key recommendations for the treatment of KD. Conditional recommendations are indicated as such and are generally conditional due to a lack of high-quality evidence (e.g., multiple randomized controlled trials) supporting the recommendation.

Treatment recommendations

Good Practice Statement: IVIG is the standard-of-care therapy for the initial treatment of KD.

IVIG has been established as the standard-of-care treatment for KD for the last 4 decades due to the significant reduction in the rate of coronary artery aneurysms as well as a reduction in the duration of fever and other symptoms associated with its use (11). Although no comparative trials of IVIG and glucocorticoids have been conducted, glucocorticoids alone were considered inadequate to treat KD based on findings from an early case series (12,13). Thus, IVIG use is a mainstay of KD therapy. The mechanisms of the therapeutic effect of IVIG in KD are still under study (14).

Recommendation: For patients with acute KD who are at high risk of IVIG resistance or developing coronary artery aneurysms, use of IVIG with adjunctive glucocorticoids as initial therapy is conditionally recommended over treatment with IVIG alone.

Risk scores have been developed to identify patients at high risk of IVIG resistance in Japanese populations, but these scores had poor sensitivity and specificity in a multiethnic US population (15–17). A recent study of patients in North America identified the following demographic and clinical characteristics as predictors for the development of coronary artery aneurysms at 2–8 weeks: a Z score in the left anterior descending or right coronary artery of ≥2.0, age <6 months, Asian race, and a C-reactive protein level of ≥13 mg/dl (18). In the US, features that suggest an increased likelihood of morbidity in KD include age <6 months or >9 years at diagnosis (19,20). In patients with giant aneurysms (Z score >10) or multiple aneurysms, regression of the aneurysms (via remodeling) at late stages (21) is less likely, and large aneurysms are associated with the greatest morbidity rate (21,22).

Emerging evidence suggests that adding glucocorticoids to IVIG as primary therapy can decrease the risk of developing coronary artery aneurysms, although the strongest evidence is from a Japanese population (16). There is also emerging evidence that the addition of glucocorticoids can decrease the progression of coronary artery aneurysms in patients with coronary aneurysms at the time of diagnosis (23,24).

Thus, the use of glucocorticoids with IVIG is a treatment option in patients who are at high risk of coronary artery aneurysms. For this recommendation, the Voting Panel defined high-risk features as a Z score of ≥2.5 (25–27) for the left anterior descending or right coronary artery at the time of the initial echocardiography and age <6 months. This definition uses the Z score of 2.5 instead of 2.0, since a score of 2.5 is defined as representing a true aneurysm. We also do not include patients >9 years of age, as only a portion of these patients are believed to be "high-risk." The Voting Panel acknowledges that further investigation clarifying the features of "high-risk" KD in a US population is needed. Optimal dosing and duration of glucocorticoids are still to be determined and will require further study in a US population, but a typical dosage would be prednisone starting at 2 mg/kg/day (maximum 60 mg/day), with the dose tapered over 15 days. The use of IVIG alone is conditionally recommended when the treating physician is unsure whether a patient is at high risk of developing coronary artery aneurysms, or when additional glucocorticoid exposure may be detrimental to the patient. The use of glucocorticoids is generally *not* recommended in patients who do not have features suggestive of high risk.

Recommendation: For patients with acute KD who are at high risk of IVIG resistance or developing coronary artery aneurysms, using IVIG with other nonglucocorticoid immunomodulatory immunosuppressive agents as initial therapy is conditionally recommended over treatment with IVIG alone.

For patients with features of high-risk disease, adjunctive therapy with a nonglucocorticoid immunomodulatory agent, such as infliximab, anakinra, or cyclosporine, may improve outcomes in acute disease and may also improve cardiac outcomes

Table 2. Good practice statement, recommendations, and ungraded position statement regarding diagnostic testing for and treatment of KD*

	KD PICO question informing recommendation and discussion	Level of evidence
Treatment recommendations		
Good practice statement: IVIG is the standard-of-care therapy for the initial treatment of KD.	3	High
For patients with acute KD who are at high risk of IVIG resistance or developing coronary artery aneurysms, use of IVIG with adjunctive glucocorticoids as initial therapy is **conditionally** recommended over treatment with IVIG alone.	4	Low
For patients with acute KD who are at high risk of IVIG resistance or developing coronary artery aneurysms, using IVIG with other nonglucocorticoid immunomodulatory immunosuppressive agents as initial therapy is **conditionally** recommended over treatment with IVIG alone.	5	Very low
For patients with incomplete KD, prompt treatment with IVIG at the time of diagnosis is **strongly** recommended over delaying treatment until day 10 or later.	1	Low
For patients with acute KD and suspected or diagnosed MAS, treatment with IVIG for KD and additional agents to treat MAS is **strongly** recommended.	2	Very low
For patients with acute KD and persistent fevers after initial treatment with IVIG, a second course of IVIG is **conditionally** recommended over the use of glucocorticoids.	10	Very low
Ungraded position statement: For patients with acute KD and persistent fevers after repeated treatment with IVIG, either nonglucocorticoid immunosuppressive therapy or glucocorticoids may be used.	11	Low
For patients with acute KD, using aspirin is **strongly** recommended over no aspirin.	6	Very low
For patients with acute KD with subsequent resolution of fevers, continued daily monitoring for fevers is **strongly** recommended over not monitoring for fevers.	12	Very low
For patients with acute KD who have arthritis that persists after IVIG treatment and who do not have coronary artery aneurysms, using NSAIDs to treat arthritis is **conditionally** recommended over not using NSAIDS.	13	Very low
Diagnostic imaging		
For children with suspected incomplete KD and fever, obtaining an echocardiogram with coronary artery measurements without delay is **strongly** recommended over not obtaining an echocardiogram.	D1	Very low
For children with unexplained shock physiology, obtaining an echocardiogram with coronary artery measurements is **strongly** recommended.	D2	Very low
For children with unexplained MAS, obtaining an echocardiogram with coronary artery measurements is **strongly** recommended.	D3	Very low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for Kawasaki disease (KD), please refer to Supplementary Appendix 2 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42041/abstract). IVIG = intravenous immunoglobulin; MAS = macrophage activation syndrome; NSAIDs = nonsteroidal antiinflammatory drugs.

(21,23,28,29). Thus, adjunctive therapy with a nonglucocorticoid immunomodulatory agent can be considered in patients with KD who are at high risk of not responding to IVIG. For any patient considered to have features of high-risk disease, a rheumatologist or other clinician with expertise in KD should be consulted before adding an adjunctive agent (glucocorticoids or nonglucocorticoid immunomodulatory agents) to ensure correct diagnosis and appropriate utilization of adjunctive therapies. The Voting Panel also advocated for a stepwise therapeutic algorithm, in which either a glucocorticoid or nonglucocorticoid immunosuppressive agent along with IVIG is initially prescribed in high-risk patients. Currently, there is more evidence supporting the use of glucocorticoids than nonglucocorticoid immunosuppressive agents in this patient population, and further study is warranted to compare the efficacy of glucocorticoid therapy to nonglucocorticoid therapy in this population. There may be specific situations in which glucocorticoids are contraindicated, but the patient exhibits high-risk features that would indicate the need for adjunctive nonglucocorticoid immunomodulatory therapy. Once again, use of IVIG alone is appropriate if the treating physician is unsure whether a patient has high-risk features, as described in the previous recommendation, or if using a nonglucocorticoid immunomodulatory agent presents a greater risk of an adverse effect to the patient.

Recommendation: For patients with incomplete KD, prompt treatment with IVIG at the time of diagnosis is strongly recommended over delaying treatment until day 10 or later.

Incomplete KD is defined as a condition of suspected KD that lacks the sufficient number of features to meet criteria for KD (3,30) (Table 1). Patients with incomplete KD should be evaluated using the algorithm for incomplete KD as outlined in the AHA guidelines for KD (3,30). The performance of this algorithm for identifying patients with incomplete KD has been validated (30). The practice of completing diagnostic testing and initiating treatment

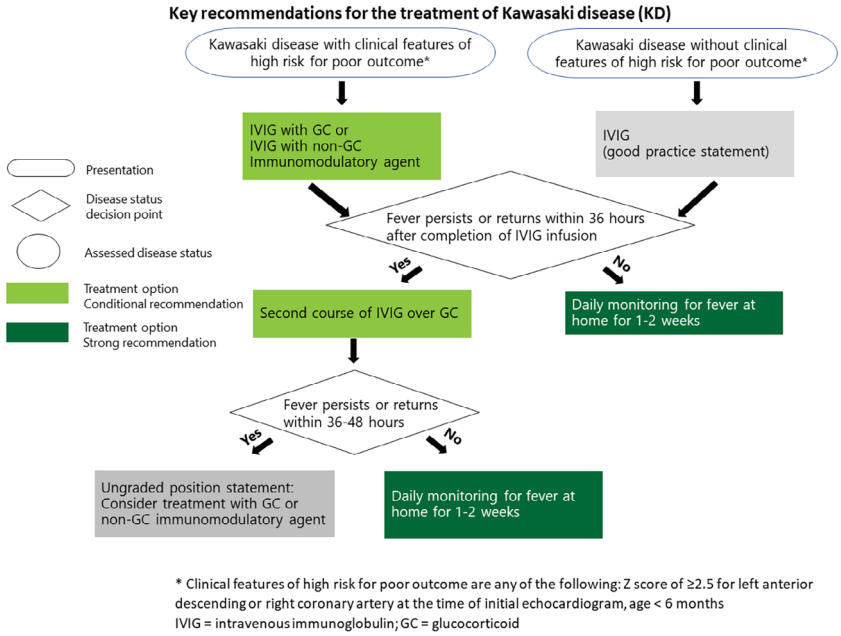
Key recommendations for the treatment of Kawasaki disease (KD)
Kawasaki disease with clinical features of high risk for poor outcome*
Kawasaki disease without clinical features of high risk for poor outcome*
IVIG with GC or IVIG with non-GC Immunomodulatory agent
IVIG (good practice statement)
Presentation
Disease status decision point
Assessed disease status
Treatment option Conditional recommendation
Treatment option Strong recommendation
Fever persists or returns within 36 hours after completion of IVIG infusion
Yes
No
Second course of IVIG over GC
Daily monitoring for fever at home for 1-2 weeks
Fever persists or returns within 36-48 hours
Yes
No
Ungraded position statement: Consider treatment with GC or non-GC immunomodulatory agent
Daily monitoring for fever at home for 1-2 weeks
* Clinical features of high risk for poor outcome are any of the following: Z score of ≥2.5 for left anterior descending or right coronary artery at the time of initial echocardiogram, age < 6 months
IVIG = intravenous immunoglobulin; GC = glucocorticoid

Figure 1. Key recommendations for the treatment of Kawasaki disease in patients with and those without clinical features indicating a high risk for poor outcome.

by day 10 of fever is not based on mechanisms or studies of disease pathogenesis or treatment outcomes. Instead, this "treatment deadline" was chosen as a research end point in the original studies in KD (31). It is recognized that prompt treatment prevents adverse outcomes, and patients should receive treatment as soon as the diagnosis of incomplete KD is made, rather than waiting until day 10 to see if they meet criteria for complete KD. Although delayed IVIG treatment after 10 days of fever is associated with worse outcomes (32), IVIG treatment should still be administered to patients even if they present after >10 days of fever. Thus, patients who meet the criteria for incomplete KD according to the AHA guidelines should be treated promptly to avoid adverse consequences, since the risk of developing coronary artery dilatation increases each day without treatment. This is a strong recommendation because this intervention is standard of care, and the consequence of delaying treatment may lead to significant coronary artery aneurysms or rupture, which are severe adverse outcomes. In addition, resolution of fever prior to day 10 is not an indication to withhold treatment in patients meeting criteria for incomplete or complete KD. In patients with characteristically elevated levels of acute-phase reactants, treatment is recommended, as these patients remain at high risk of developing adverse outcomes (3,33).

Recommendation: For patients with acute KD and suspected or diagnosed macrophage activation syndrome (MAS), treatment with IVIG for KD and additional agents to treat MAS is strongly recommended.

MAS, a form of secondary hemophagocytic lymphohistiocytosis (HLH), is a potentially underrecognized complication of KD (34,35). Formal diagnostic criteria for MAS in the setting of KD have not been developed. However, drawing on experience with other secondary HLH presentations, MAS may be suspected in KD patients with persistent fever, splenomegaly, elevated ferritin levels, and thrombocytopenia (35). Inadequate treatment of either KD or MAS could result in severe consequences. These include large coronary aneurysms or coronary artery stenosis, leading to death via cardiac infarct or coronary rupture in KD, or death due to multiorgan dysfunction in MAS (36).

Thus, to ensure appropriate therapy, each disease entity should be considered separately with appropriate targeted therapy. KD should be treated with IVIG as the first-line therapy, and MAS should also be treated with appropriate agents for targeting cytokine storm or underlying triggers. Anakinra and glucocorticoids are preferred for treatment in these patients over a primary HLH–directed treatment protocol with cytotoxic agents. Although no head-to-head comparison trials have been published, primary HLH–directed therapy, which has considerably more associated toxicity, may not be warranted in patients without an underlying genetic predisposition to HLH. This is a strong recommendation because the consequence of not appropriately treating KD or MAS may be associated with increased mortality.

Recommendation: For patients with acute KD and persistent fevers after initial treatment with IVIG, a second course of IVIG is conditionally recommended over the use of glucocorticoids.

Findings from 6 studies provide indirect evidence for this recommendation, though no direct comparative studies were available (37–42). For KD patients with persistent fevers after

the initial course of IVIG, studies suggest that there is no difference in coronary artery outcomes between repeating the course of IVIG versus a single dose of pulse glucocorticoids (i.e., 30 mg/kg with a maximum of 1 gm) (43). A meta-analysis of 12 studies involving 372 patients whose disease was resistant to treatment with a single course of IVIG failed to demonstrate significant differences in coronary artery outcomes between patients treated with a second dose of IVIG versus glucocorticoids versus infliximab (44). Although current evidence does not clearly indicate the superiority of a second course of IVIG over glucocorticoids, a second course of IVIG in patients who have persistent fever for >36 hours after the first dose is conditionally recommended, as it is the current standard of care. However, as a conditional recommendation, glucocorticoids are a reasonable alternative (e.g., starting at 2 mg/kg/day and tapering over 15 days or a single dose of 20–30 mg/kg). Repeated doses of IVIG may put patients at risk of hemolytic anemia, and the results of ongoing studies may alter this recommendation in the future (45–47). In patients with risk factors for hemolytic anemia with IVIG, such as non–type O blood groups, alternative therapies, such as glucocorticoids or nonglucocorticoid immunomodulatory therapy, should be considered (45,48). Combination therapy (i.e., multiple anticytokine agents) is not recommended for routine care and generally should only be considered in patients with extremely severe disease.

Ungraded Position Statement: For patients with acute KD and persistent fevers after repeated treatment with IVIG, either nonglucocorticoid immunosuppressive therapy or glucocorticoids may be used.

In patients with KD and persistent fevers after 2 doses of IVIG, use of another agent is indicated. Findings from studies of infliximab and cyclosporine for the treatment of refractory KD suggest some potential benefit of these agents (28,29). Head-to-head comparisons between these nonglucocorticoid immunosuppressive agents and glucocorticoids have not been performed. There is no clinical evidence to suggest superiority of either glucocorticoids or nonglucocorticoid immunomodulatory agents, and the Voting Panel was evenly split as to which to recommend. Thus, the Voting Panel believes that use of either class of agents would be appropriate based on the specific clinical scenario. Combination therapy (glucocorticoid with a nonglucocorticoid immunosuppressive agent) can be considered in severe cases, such as rapidly expanding aneurysms or imminently life-threatening disease.

Recommendation: For patients with acute KD, using aspirin is strongly recommended over no aspirin.

The use of aspirin in patients with KD to reduce inflammation and prevent thrombosis through its antiplatelet effect is considered standard of care. However, the optimal dosage is unclear. Historically, high dosages of aspirin (80–100 mg/kg/day) were used during the acute phase for antiinflammatory effects, but there is no evidence of benefit with high- versus low-dose aspirin (3–5 mg/kg/day) when considering coronary vascular damage (49–51). The AHA guidelines should be consulted for recommendations regarding anticoagulation in patients with larger aneurysms (3). This is a strong recommendation because aspirin is recognized to be a low-cost intervention with limited toxicity at antiplatelet dosing, and also because there are significant consequences of not inhibiting platelet activity, such as coronary artery thrombosis.

Recommendation: For patients with acute KD with subsequent resolution of fevers, continued daily monitoring is strongly recommended over not monitoring for fevers.

Patients with KD may experience recurrence of disease or treatment-refractory disease heralded by returning fever and other symptoms. In addition, the duration of fever is a predictor of coronary artery aneurysms (52). Thus, patients should be monitored daily for fevers for 1–2 weeks after discharge, with fever defined as an oral temperature in older children and a rectal temperature in infants of >38.0°C or an axillary temperature of >37.5°C. Parents or guardians should be instructed by the discharging physician on how to take a temperature and told to contact the physician should fever recur. Daily fever monitoring is strongly recommended because it is low cost, without harms, and may identify recurring KD.

Recommendation: For patients with acute KD who have arthritis that persists after IVIG treatment and who do not have coronary artery aneurysms, using nonsteroidal antiinflammatory drugs (NSAIDs) to treat arthritis is conditionally recommended over not using NSAIDS.

Patients with acute and subacute KD can develop arthritis, but treatment with IVIG decreases the incidence of arthritis in this setting from 30% to ~2–12% (53). Arthritis in KD is usually short-lived, lasting between 7 and 21 days (53–55). In general, arthritis can be treated with NSAIDs, but NSAIDs directly inhibit the ability of aspirin to acetylate cyclooxygenase 1, thus decreasing aspirin's protective effects (56). The impact of NSAID use can be partially mitigated by administering aspirin prior to NSAIDs, but combination therapy is usually not recommended given the potential increased toxicity (56).

Patients without coronary artery aneurysms generally do not require long-term treatment with aspirin. The optimal duration of treatment with aspirin in these patients is not well defined but in practice is generally 6–8 weeks. Patients with coronary artery aneurysms require long-term and potentially indefinite aspirin use (3). For patients *without* coronary artery aneurysms who do not require long-term use of aspirin and who have arthritis requiring additional therapy, aspirin can be temporarily suspended and a short course (3–4 weeks) of NSAIDs can be used as needed.

Conversely, if indefinite or long-term aspirin use is needed due to coronary artery aneurysms, then either acetaminophen, a short course of glucocorticoids, or nonsystemic NSAID pain management options (e.g., a topical NSAID) can be used. A pediatric hematologist or cardiologist should be consulted to consider an alternative anticoagulant (e.g., clopidogrel) if prolonged use of systemic NSAIDs is required (i.e., >3 weeks), especially in a patient with coronary artery aneurysms.

Diagnostic imaging

Recommendation: For children with suspected incomplete KD and fever, obtaining an echocardiogram with coronary artery measurements without delay is strongly recommended over not obtaining an echocardiogram.

Patients with incomplete KD have at least the same or an increased risk of coronary artery lesions compared to patients with classic KD (57). Therefore, in patients in whom incomplete KD is suspected, a diagnosis should be confirmed as soon as possible so that features associated with high risk of coronary artery aneurysms can be assessed, treatment can be initiated without delay, and adverse outcomes can be prevented. Echocardiographic assessment of the absolute dimensions of the coronary artery and body surface area–adjusted Z scores can help establish a diagnosis of incomplete KD and should be obtained promptly when this diagnosis is suspected. The AHA guidelines for KD management provide an algorithm for the evaluation and treatment of suspected incomplete KD (3), which has been validated (30). Echocardiography is strongly recommended in this scenario because it has minimal potential harms and may prevent adverse outcomes by prompting the treatment of incomplete KD.

Recommendation: For children with unexplained shock physiology, obtaining an echocardiogram with coronary artery measurements is strongly recommended.

Unexplained shock can be due to Kawasaki shock syndrome, a recognized manifestation of KD (58). Echocardiograms are often obtained in children with unexplained shock, especially in those with the prodrome of prolonged fever, to evaluate cardiac function and help identify the potential etiology. We recommend that the coronary arteries be included in the echocardiographic examination to evaluate for KD as a potential etiology of shock. This is strongly recommended because echocardiography has minimal potential harms and may prevent catastrophic outcomes by facilitating the diagnosis and prompt treatment of KD.

Recommendation: For children with unexplained MAS, obtaining an echocardiogram with coronary artery measurements is strongly recommended.

As noted above, KD is one of the clinical inflammatory entities that can predispose patients to the development of MAS (59). For patients with unexplained MAS, KD should be considered as a potential underlying etiology. Echocardiography with inclusion of the coronary arteries is one method of identifying KD as a potential treatable underlying condition. This is strongly recommended because echocardiography has minimal potential harms and may prevent adverse outcomes by facilitating the diagnosis and prompt treatment of KD.

DISCUSSION

This is the first guideline issued by the ACR in conjunction with the Vasculitis Foundation for the management of KD. These recommendations constitute a guide to help physicians treat KD. This guideline should not be used by any agency to restrict access to therapy or require that certain therapies must be utilized prior to other therapies.

Patients with KD in the US are often diagnosed and treated by physicians with expertise in areas other than rheumatology (e.g., pediatric cardiologists, hospitalists, or infectious disease specialists). The recommendations in this guideline focus on situations in which rheumatologists are often consulted, such as in the management of severe disease, treatment-refractory disease, arthritis, and MAS with KD. However, these recommendations are relevant to physicians treating KD regardless of their area of expertise.

The AHA has presented recommendations for the initial treatment and long-term management of KD (3). Recommendations presented in this guideline are intended to supplement the AHA guidelines and serve as an additional reference for rheumatologists who may be less familiar with KD. Emerging evidence suggesting that adjunctive therapy decreases the incidence of severe coronary artery aneurysms and accelerates regression of these aneurysms provides the basis for the recommendations concerning "high-risk" KD (23). Although aneurysms that have regressed are affected by endothelial dysfunction and therefore remain abnormal vasculature, normalized vessel caliber decreases the risk of morbidity from vessel thrombosis (3).

Finally, during the COVID-19 pandemic, a novel multisystem inflammatory syndrome in children (MIS-C) associated with SARS–CoV-2 infection emerged, with some features suggestive of KD (60,61). While as many as 50% of these patients could meet criteria for KD, many patients exhibit manifestations that are unusual for KD, including colitis, myocarditis, and neurologic changes, and often present with or develop shock (62). Further study is needed to understand the relationship between MIS-C and KD, especially Kawasaki shock syndrome. Based on clinical experience, recognition and differentiation of these patients from patients with classic KD is important. Patients who fulfill criteria for KD should be treated using the therapies discussed in this guideline. Additional research is needed to

determine optimal treatment for MIS-C with and without KD features.

In summary, the ACR and Vasculitis Foundation present these recommendations to assist physicians in managing KD. This guideline can serve as a resource for basic principles of management and will evolve as new treatment strategies for this disease are identified.

ACKNOWLEDGMENTS

We thank Anne M. Ferris, MBBS, Ora Gewurz-Singer, MD, Rula Hajj-Ali, MD, Eric Matteson, MD, MPH, Robert F. Spiera, MD, Linda Wagner-Weiner, MD, MS, and Kenneth J. Warrington, MD, for serving on the Expert Panel. We thank Antoine G. Sreih, MD and Gary S. Hoffman, MD, MS, for their contributions during the early phases of this project as members of the Core Team. Dr. Hoffman's participation ended July 2018 due to personal reasons. Dr. Sreih's involvement ended in December 2018 when he became primarily employed by industry, which precluded his continued participation in this project. We thank Joyce Kullman (Vasculitis Foundation) for her assistance with recruitment for the Patient Panel. We thank the patients who (along with authors Kathy A. Full and Omar I. Vitobaldi) participated in the Patient Panel meeting: Jane Ascroft, Scott A. Brunton, Dedra DeMarco, Thomas Fitzpatrick, Jenn Gordon, Maria S. Mckay, Sandra Nye, Stephanie Sakson, and Ben Wilson. We thank Robin Arnold, Catherine E. Najem, MD, MSCE, and Amit Aakash Shah, MD, MPH, for their assistance with the literature review. We thank the ACR staff, including Ms. Regina Parker, for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, and Ms. Cindy Force for assistance in manuscript preparation. We thank Ms. Janet Waters for help in developing the literature search strategy and performing the initial literature search, and Ms. Janet Joyce for performing the update searches.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Chung had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Gorelik, Chung, Friedman, Sule, Yildirim-Toruner, Langford, Maz, Abril, Guyatt, Full, Stone, Sundel, Vitobaldi, Husainat, Turgunbaev, Turner, Mustafa.

Acquisition of data. Gorelik, Chung, Binstadt, Lapidus, Kim, Sule, Yildirim-Toruner, Full, Grayson, Stone, Sundel, Byram, Dua, Husainat, James, Kalot, Lin, Springer, Turgunbaev, Villa-Forte, Mustafa.

Analysis and interpretation of data. Gorelik, Chung, Ardalan, Binstadt, Hayward, Imundo, Lapidus, Kim, Son, Sule, Tremoulet, Van Mater, Yildirim-Toruner, Abril, Archer, Conn, Full, Grayson, Ibarra, Merkel, Rhee, Seo, Stone, Sundel, Warner, Byram, Dua, Husainat, Kalot, Lin, Springer, Turgunbaev, Villa-Forte, Mustafa.

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Arthritis & Rheumatology
Vol. 74, No. 3, March 2022, pp 400–406
DOI 10.1002/art.41983
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2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Microscopic Polyangiitis

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European Alliance of Associations for Rheumatology (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

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Objective. To develop and validate classification criteria for microscopic polyangiitis (MPA).

Methods. Patients with vasculitis or comparator diseases were recruited into an international cohort. The study proceeded in 5 phases: 1) identification of candidate items using consensus methodology, 2) prospective collection of candidate items present at the time of diagnosis, 3) data-driven reduction of the number of candidate items, 4) expert panel review of cases to define the reference diagnosis, and 5) derivation of a points-based risk score for disease classification in a development set using least absolute shrinkage and selection operator logistic regression, with subsequent validation of performance characteristics in an independent set of cases and comparators.

Results. The development set for MPA consisted of 149 cases of MPA and 408 comparators. The validation set consisted of an additional 142 cases of MPA and 414 comparators. From 91 candidate items, regression analysis identified 10 items for MPA, 6 of which were retained. The final criteria and their weights were as follows: perinuclear antineutrophil cytoplasmic antibody (ANCA) or anti–myeloperoxidase-ANCA positivity (+6), pauci-immune glomerulonephritis (+3), lung fibrosis or interstitial lung disease (+3), sino-nasal symptoms or signs (−3), cytoplasmic ANCA or anti–proteinase 3 ANCA positivity (−1), and eosinophil count ≥1 × 10^9/liter (−4). After excluding mimics of vasculitis, a patient with a diagnosis of small- or medium-vessel vasculitis could be classified as having MPA with a cumulative score of ≥5 points. When these criteria were tested in the validation data set, the sensitivity was 91% (95% confidence interval [95% CI] 85–95%) and the specificity was 94% (95% CI 92–96%).

Conclusion. The 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for MPA are now validated for use in clinical research.

This article is published simultaneously in the March 2022 issue of *Annals of the Rheumatic Diseases*.

The Diagnostic and Classification Criteria in Vasculitis (DCVAS) study, of which the development of these classification criteria was a part, was funded by grants from the American College of Rheumatology (ACR), the European Alliance of Associations for Rheumatology (EULAR), the Vasculitis Foundation, and the University of Pennsylvania Vasculitis Center.

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INTRODUCTION

The first description of "periarteritis nodosa" was made by Kussmaul and Maier in 1866 (1). In 1948, Davson et al described 14 cases at autopsy that fitted the clinical description of periarteritis nodosa (2). They divided the cases into 2 groups based on the histologic findings in the kidneys. The clinical presentations of both groups were similar, but their pathologic features differed: 9 patients showed a distinctive pattern of necrotizing glomerulonephritis with no arterial aneurysms, whereas the other 5 patients showed no glomerular lesions in the kidney but had widespread renal arterial aneurysms and renal infarcts. This is the first time that a clear distinction was made between the microscopic form of polyarteritis nodosa (now called microscopic polyangiitis [MPA]) and classic polyarteritis nodosa (PAN). The 1990 American College of Rheumatology (ACR) criteria for the classification of vasculitis did not make this distinction; instead both entities were included under the term "polyarteritis nodosa" (3) or possibly "granulomatosis with polyangiitis" (then called Wegener's granulomatosis).

The publication that resulted from the 1994 Chapel Hill Consensus Conference (CHCC) aimed to standardize the nomenclature and commented that "different names are being used for the same disease and the same name is being used for different diseases" (4). The distinction between MPA and PAN is recognized in the CHCC definitions. The main discriminating feature between MPA and PAN is the presence in MPA of pauci-immune vasculitis in arterioles, venules, or capillaries. PAN is restricted to a medium-vessel disease, and MPA is a predominantly small-vessel vasculitis that can also involve medium-sized vessels.

The resulting inconsistency between disease definitions and existing classification criteria highlights an important need to update the classification criteria and to include MPA as its own entity. Additionally, over time there have been improvements in our understanding of the different forms of vasculitis, which have been informed in part by routine testing for antineutrophil cytoplasmic antibody (ANCA) in patients with vasculitis and increased utilization of cross-sectional imaging, both of which have occurred since the 1990 ACR criteria were published. Indeed, most investigators regard MPA as part of the group of small-vessel vasculitides related to the presence of ANCA. This article outlines the development and validation of the new ACR/European Alliance of Associations for Rheumatology (EULAR)–endorsed classification criteria for MPA.

METHODS

A detailed and complete description of the methods involved in the development and validation of the classification criteria for MPA is provided in Supplementary Appendix 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41983/abstract. Briefly, an international Steering Committee comprising clinician investigators with expertise in vasculitis, statisticians, and data managers was established to oversee the overall Diagnostic and Classification Criteria in Vasculitis (DCVAS) project. The Steering Committee established a 5-stage plan using data-driven and consensus methodology to develop the criteria for each of 6 forms of vasculitis.

Stage 1: generation of candidate classification items for the systemic vasculitides. Candidate classification items were generated by expert opinion and reviewed by a group of vasculitis experts across a range of specialties using a nominal group technique.

Stage 2: DCVAS prospective observational study. A prospective, international multisite observational study was conducted (see Appendix A for study investigators and sites). Ethical approval was obtained from national and local ethics committees. Consecutive patients representing the full spectrum of disease were recruited from academic and community practices. Patients were included if they were 18 years or older and had a diagnosis of vasculitis or a condition that mimics vasculitis. Patients with ANCA-associated vasculitis (AAV) could only be enrolled within 2 years of diagnosis. Only data present at diagnosis were recorded.

Stage 3: refinement of candidate items specifically for AAV. The Steering Committee conducted a data-driven process to reduce the number of candidate items of relevance to cases and comparators for AAV. Items were selected for exclusion if they had a prevalence of <5% within the data set and/or they were not clinically relevant for classification criteria (e.g., related to infection, malignancy, or demographic characteristics). Low-frequency items of clinical importance could be combined, when appropriate.

Stage 4: expert review to derive a gold standard–defined set of cases of AAV. Experts in vasculitis from a wide range of geographic locations and specialties reviewed all submitted cases of vasculitis and a random selection of mimics of

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.41983&file=art41983-sup-0001-Disclosureform.pdf.

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Submitted for publication February 28, 2020; accepted in revised form September 21, 2021.

vasculitis. Each reviewer was asked to review ~50 submitted cases to confirm the diagnosis and to specify the certainty of their diagnosis as follows: very certain, moderately certain, uncertain, or very uncertain. Only cases agreed upon with at least moderate certainty were retained for further analysis.

Stage 5: derivation and validation of the final classification criteria for MPA. The DCVAS AAV data set was randomly split into development (50%) and validation (50%) sets. Comparisons were performed between cases of MPA and a comparator group randomly selected from the DCVAS cohort in the following proportions: another type of AAV (including granulomatosis with polyangiitis [GPA] and eosinophilic granulomatosis with polyangiitis [EGPA]), 60%; another form of small-vessel vasculitis (e.g., cryoglobulinemic vasculitis) or medium-vessel vasculitis (e.g., PAN), 40%. Least absolute shrinkage and selection operator (lasso) logistic regression was used to identify items from the data set and create a parsimonious model including only the most important items. The final items in the model were formulated into a clinical risk-scoring tool with each factor assigned a weight based on its respective regression coefficient. A threshold that best balanced sensitivity and specificity was identified for classification.

In sensitivity analyses, the final classification criteria were applied to an unselected population of cases and comparators from the DCVAS data set based on the submitting physician diagnosis.

RESULTS

Generation of candidate classification items for the systemic vasculitides. The Steering Committee identified >1,000 candidate items for the DCVAS case report form (see Supplementary Appendix 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41983/abstract).

DCVAS prospective observational study. Between January 2011 and December 2017, the DCVAS study recruited 6,991 participants from 136 sites in 32 countries. Information on the DCVAS sites, investigators, and participants is listed in Supplementary Appendices 3, 4, and 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41983/abstract.

Refinement of candidate items specifically for AAV. Following a data-driven and expert consensus process, 91 items from the DCVAS case report form were retained for regression analysis, including 45 clinical (14 composite), 18 laboratory (2 composite), 12 imaging (all composite), and 16 biopsy (1 composite) items. Some clinical items were removed in favor of similar but more specific pathophysiologic descriptors. For example, "Hearing loss or reduction" was removed, and the composite item "Conductive hearing loss/sensorineural hearing loss" was retained. See Supplementary Appendix 6, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41983/abstract, for the final candidate items used in the derivation of the classification criteria for GPA, MPA, and EGPA.

Expert review to derive a gold standard–defined final set of cases of AAV. Fifty-five independent experts reviewed vignettes derived from the case report forms for 2,871 cases submitted with a diagnosis of either small-vessel vasculitis (90% of case report forms) or another type of vasculitis or a mimic of vasculitis (10% of case report forms). The characteristics of the expert reviewers are shown in Supplementary Appendix 7, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41983/abstract. A flow chart showing the results of the expert review process is shown in Supplementary Appendix 8, available on the *Arthritis &*

Table 1. Demographic and disease features of cases of MPA and comparators*

	MPA (n = 291)	Comparators (n = 822)†	*P*
Age, mean ± SD years	65.5 ± 13.2	52.0 ± 16.9	<0.001
Sex, no. (%) female	164 (56.4)	394 (47.9)	0.016
Maximum serum creatinine, mean			<0.001
μmoles/liter	126.4	185.2	
mg/dl	1.4	2.1	
cANCA positive, no. (%)	11 (3.8)	257 (31.3)	<0.001
pANCA positive, no. (%)	236 (81.1)	136 (16.5)	<0.001
Anti–PR3-ANCA positive, no. (%)	6 (2.1)	265 (32.2)	<0.001
Anti–MPO-ANCA positive, no. (%)	279 (95.9)	142 (17.3)	<0.001
Maximum eosinophil count ≥1 × 10^9/liter, no. (%)	15 (5.2)	244 (29.7)	<0.001

* cANCA = cytoplasmic antineutrophil cytoplasmic antibody; pANCA = perinuclear ANCA; anti–PR3-ANCA = anti–proteinase 3–ANCA; anti–MPO-ANCA = anti–myeloperoxidase-ANCA.
† Diagnoses of comparators for the classification criteria for microscopic polyangiitis (MPA) included granulomatosis with polyangiitis (n = 300), eosinophilic granulomatosis with polyangiitis (n = 226), polyarteritis nodosa (n = 51), non–ANCA-associated small-vessel vasculitis that could not be subtyped (n = 51), Behçet's disease (n = 50), IgA vasculitis (n = 50), cryoglobulinemic vasculitis (n = 34), ANCA-associated vasculitis that could not be subtyped (n = 25), primary central nervous system vasculitis (n = 19), and anti–glomerular basement membrane disease (n = 16).

Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41983/abstract. A total of 2,072 cases (72%) passed the process and were designated as cases of vasculitis; these cases were used for the stage 5 analyses.

After expert panel review by 55 investigators, 269 of 404 of the cases retained the submitting physician diagnosis of MPA, and 22 additional cases were reclassified as having MPA by consensus of 2 expert reviewers. Compared to the 291 patients with a reference diagnosis of MPA, the 135 cases that were excluded had lower rates of perinuclear ANCA (pANCA) or anti–myeloperoxidase-ANCA (anti–MPO-ANCA) positivity (76% versus 98%; $P < 0.01$), were less likely to have pauci-immune glomerulonephritis (16% versus 49%; $P < 0.01$), were more likely to have maximum eosinophil counts $\geq 1 \times 10^9$/liter (12% versus 6%; $P = 0.02$), and were more likely to be cytoplasmic ANCA– or proteinase 3–ANCA–positive (20% versus 4%; $P < 0.01$). There were 822 comparators randomly selected for analysis. Table 1 shows the demographic and disease features of the 1,113 cases included in this analysis (291 patients with MPA and 822 comparators), of which 557 (50%; 149 patients with MPA and 408 comparators) were in the development set, and 556 (50%; 142 patients with MPA and 414 comparators) were in the validation set.

Derivation and validation of the final classification criteria for MPA. Lasso regression of the previously selected 91 items yielded 10 independent items for MPA (see Supplementary Appendix 9C, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41983/abstract). Each item was then adjudicated by the DCVAS Steering Committee for inclusion based on clinical relevance and specificity to MPA, resulting in 6 final items. Weighting of an individual criterion was based on logistic regression fitted to the 6 selected items (see Supplementary Appendix 10C, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41983/abstract).

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

CLASSIFICATION CRITERIA FOR **MICROSCOPIC POLYANGIITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify a patient as having microscopic polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

CLINICAL CRITERIA

Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage or septal defect / perforation	-3

LABORATORY, IMAGING, AND BIOPSY CRITERIA

Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies ANCA positive	+6
Fibrosis or interstitial lung disease on chest imaging	+3
Pauci-immune glomerulonephritis on biopsy	+3
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-1
Blood eosinophil count ≥ 1 x10^9/liter	-4

Sum the scores for 6 items, if present. A score of ≥ 5 is needed for classification of MICROSCOPIC POLYANGIITIS.

Figure 1. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis.

Model performance. Use of a cutoff of ≥5 in total risk score (see Supplementary Appendix 11C, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41983/abstract, for different cut points) yielded a sensitivity of 90.8% (95% confidence interval [95% CI] 84.9–95.0%) and a specificity of 94.2% (95% CI 91.5–96.3%) in the validation set. The area under the curve for the model was 0.98 (95% CI 0.97–0.99) in the development set and 0.97 (95% CI 0.95–0.98) in the validation set for the final MPA classification criteria (Supplementary Appendix 12C, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41983/abstract). The final classification criteria for MPA are shown in Figure 1 (for the slide presentation version, see Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41983/abstract).

Sensitivity analysis. The classification criteria for MPA were applied to 2,871 patients in the DCVAS database using the original physician-submitted diagnosis (n = 404 cases of MPA and 2,467 randomly selected comparators). Use of the same cut point of ≥5 points for the classification for MPA yielded a similar specificity of 92.5% but a lower sensitivity of 82.4%. This is consistent with the a priori hypothesis that specificity would remain unchanged but sensitivity would be reduced in a population with fewer clearcut diagnoses of MPA (i.e., cases that did not pass expert panel review).

DISCUSSION

Presented here are the 2022 ACR/EULAR MPA classification criteria. These are the first formal criteria for MPA. A 5-stage approach has been used, underpinned by data from the multinational prospective DCVAS study and informed by expert review and consensus at each stage. The comparator group for developing and validating the criteria were predominantly patients with other forms of AAV and other small- and medium-vessel vasculitides, the clinical entities where discrimination from MPA is difficult, but important. The new criteria for MPA have excellent sensitivity and specificity and incorporate ANCA testing and modern imaging techniques. The criteria were designed to have face and content validity for use in clinical trials and other research studies.

These criteria are validated and intended for the purpose of *classification* of vasculitis and are not appropriate for use in establishing a *diagnosis* of vasculitis. The aim of the classification criteria is to differentiate cases of MPA from similar types of vasculitis in research settings. Therefore, the criteria should only be applied when a diagnosis of small- or medium-vessel vasculitis has been made and all potential "vasculitis mimics" have been excluded. The exclusion of mimics is a key aspect of many classification criteria, including those for Sjögren's syndrome (5) and rheumatoid arthritis (6). The 1990 ACR classification criteria for vasculitis perform poorly when used for diagnosis (i.e., when used to differentiate between cases of vasculitis versus mimics without vasculitis) (7), and it is expected that the 2022 criteria would also perform poorly if used inappropriately as diagnostic criteria in people in whom alternative diagnoses, such as infection or other non-vasculitis inflammatory diseases, are still being considered. The relatively low weight assigned to glomerulonephritis in these classification criteria highlights the distinction between classification and diagnostic criteria. While detection of kidney disease is important to diagnose MPA, glomerulonephritis is common among patients with either GPA or MPA and thus does not function as a strong classifier between these conditions.

MPA was not recognized as a separate entity in the 1990 ACR classification criteria for vasculitis, although the disease was recognized as pathologically distinct from PAN over 40 years earlier. This omission of MPA caused difficulties in defining clear homogeneous populations for research; thus, over the last 2 decades, investigators have often relied on the disease definitions of the CHCC nomenclature for eligibility criteria when enrolling patients with MPA into clinical trials (4,8–11). This approach resulted in heterogeneity between patients enrolled in therapeutic trials and epidemiologic studies (12). Due to inconsistent methods employed by researchers when applying the 1990 ACR criteria and the CHCC definitions in parallel, the European Medicines Agency (EMA) convened meetings to develop a consensus on how to utilize the 2 systems, leading to the publication of the EMA algorithm in 2007 (13). The algorithm works by first excluding EGPA and GPA, and then relying on the CHCC histologic descriptions to discriminate between MPA and PAN. The new 2022 ACR/EULAR classification criteria for MPA and other vasculitides provide validated criteria that can replace the EMA interim solution and should harmonize future research studies.

A potential limitation of these new criteria is that, through the expert panel consensus methodology, only the most definite cases were included in the analyses. However, the purpose of these criteria is to enable homogeneous groupings so that individual diseases can be studied. Overall, the use of more definitive cases is consistent with the purpose of classification criteria. Additionally, positive testing for MPO-ANCA is weighted heavily in the criteria, and it is theoretically possible to classify a patient as having MPA on the basis of a positive test for MPO-ANCA only. However, the criteria are intended to only be applied to patients with an established diagnosis of small- or medium-vessel vasculitis; in this setting, the criteria sets should result in a reduction of the score away from a classification of MPA if the patient has features of another form of AAV. When criteria were tested in a much less clearly defined population using the submitting physician diagnosis as the gold standard, the sensitivity of the criteria fell substantially despite 91% of this group being pANCA- or MPO-ANCA positive, which supports the contention that ANCA positivity is not overly dominant for the classification. Nonetheless, ANCA testing is obviously a key discriminator between the different forms of AAV and other small- and medium-vessel vasculitides.

There are some additional study limitations to consider. Although this was the largest international study ever conducted in vasculitis, most patients were recruited from Europe, Asia, and North America. The performance characteristics of the criteria should be further tested in African and South American populations, which may have different clinical presentations of vasculitis. These criteria were developed using data collected from adult patients with vasculitis. Although the clinical characteristics of MPA and the other vasculitides which these criteria were tested against are not known to differ substantially between adults and children, these criteria should be applied to children with some caution. The scope of the criteria is intentionally narrow and applies only to patients who have been diagnosed as having vasculitis. Diagnostic criteria are not specified. The criteria are intended to identify homogeneous populations of disease and, therefore, may not be appropriate for studies focused on the full spectrum of clinical heterogeneity in these conditions. To maximize relevance and face validity of the new criteria, study sites and expert reviewers were recruited from a broad range of countries and different medical specialties. Nonetheless, the majority of patients were recruited from academic rheumatology or nephrology units, which could have introduced referral bias.

The 2022 ACR/EULAR classification criteria for MPA are the product of a rigorous methodologic process that utilized an extensive data set generated by the work of a remarkable international group of collaborators. These are the first classification criteria for this disease. The criteria can now be applied to patients who have been diagnosed as having a small- or medium-vessel vasculitis. These criteria have been endorsed by the ACR and EULAR and are now ready for use to differentiate one type of vasculitis from another to define populations in research studies.

ACKNOWLEDGMENTS

We acknowledge the patients and clinicians who provided data to the DCVAS project.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Merkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Arthritis Care & Research
Vol. 73, No. 8, August 2021, pp 1061–1070
DOI 10.1002/acr.24633
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American College of Rheumatology
Empowering Rheumatology Professionals

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions, and drug formularies or other third-party analyses that cite ACR guidelines should state this. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

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Objective. To provide evidence-based recommendations and expert guidance for the management of systemic polyarteritis nodosa (PAN).

Methods. Twenty-one clinical questions regarding diagnostic testing, treatment, and management were developed in the population, intervention, comparator, and outcome (PICO) format for systemic, non–hepatitis B–related PAN. Systematic literature reviews were conducted for each PICO question. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to assess the quality of evidence and formulate recommendations. Each recommendation required ≥70% consensus among the Voting Panel.

Results. We present 16 recommendations and 1 ungraded position statement for PAN. Most recommendations were graded as conditional due to the paucity of evidence. These recommendations support early treatment of severe PAN with cyclophosphamide and glucocorticoids, limiting toxicity through minimizing long-term exposure to both treatments, and the use of imaging and tissue biopsy for disease diagnosis. These recommendations endorse minimizing risk to the patient by using established therapy at disease onset and identify new areas where adjunctive therapy may be warranted.

Conclusion. These recommendations provide guidance regarding diagnostic strategies, use of pharmacologic agents, and imaging for patients with PAN.

The article is published simultaneously in *Arthritis & Rheumatology*.
Supported by the American College of Rheumatology and the Vasculitis Foundation.

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INTRODUCTION

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that primarily affects medium-sized vessels (1). Patients frequently present with systemic symptoms such as fever and weight loss. The most common clinical presentations include neurologic manifestations such as mononeuritis multiplex and peripheral neuropathy, cutaneous manifestations such as nodules and livedo reticularis, renal manifestations such as hypertension, and gastrointestinal manifestations such as abdominal pain (2). Diagnosis is generally confirmed by tissue biopsy of an affected organ or angiography if tissue biopsy cannot be obtained. Typical histologic findings include mixed-cell inflammatory infiltrates in the vessel wall and fibrinoid necrosis, with an absence of granulomas and giant cells (3). Findings on angiography include saccular or fusiform aneurysms and stenotic lesions in the mesenteric, hepatic, and renal arteries and their subsequent branches. Although PAN is becoming increasingly rare due to the prevention of hepatitis B viral (HBV) infection, it remains a potentially devastating diagnosis, with severe PAN having a mortality rate of 40% at 5 years (3).

Given the increasing options available to treat systemic vasculitis, the American College of Rheumatology (ACR) and the Vasculitis Foundation (VF) supported the development of guidelines for the management of large, medium, and small vessel vasculitis. This guideline presents evidence-based recommendations for the diagnostic testing, treatment, and management of PAN as an exemplar of medium vessel vasculitis. Of note, this guideline focuses on systemic PAN. Since HBV-associated PAN as well as cutaneous PAN are generally managed differently from systemic idiopathic PAN, they were excluded from this guideline.

Although this guideline may inform an international audience, these recommendations were developed considering the experience with and availability of treatment and diagnostic options in the US.

METHODS

This guideline followed the ACR guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and develop recommendations (4,5). ACR policy guided the management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis). Supplementary Appendix 1 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24633/abstract) presents a detailed description of the methods. Briefly, the Literature Review team undertook systematic literature reviews for predetermined questions specifying the clinical population, intervention, comparator, and outcomes (PICO). An in-person Patient Panel of 11 individuals with different types of vasculitis (1 patient with PAN) was moderated by a member of the Literature Review team (ABD). This Patient Panel reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives and preferences. An Expert Panel provided expert knowledge to inform discussion of the PICO questions and findings of the literature review. The Voting Panel comprised 9 adult rheumatologists, 5 pediatric rheumatologists, and 2 patients; they reviewed the Literature Review team's evidence summaries and, bearing in mind the Patient Panel's deliberations, formulated and voted on recommendations. A recommendation required ≥70% consensus among the Voting Panel.

How to interpret the recommendations

A *strong* recommendation is typically supported by moderate- to high-quality evidence (e.g., multiple randomized controlled

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Dr. Langford has received consulting fees, speaking fees, and/or honoraria from Bristol Myers Squibb (less than $10,000) and research grants from Bristol Myers Squibb, GlaxoSmithKline, and Genentech. Dr. Grayson has submitted a patent application for the diagnosis and treatment of vacuoles, E1 enzyme, x-linked, autoinflammatory, somatic (VEXAS) syndrome. Dr. Merkel has received consulting fees, speaking fees, and/or honoraria from AbbVie, Biogen, Bristol Myers Squibb, CSL Behring, Genentech/Roche, Genzyme/GlaxoSmithKline, Insmed, Janssen, Kiniksa, Kyverna, Pfizer, Sparrow, and Takeda (less than $10,000 each) and from AstraZeneca, InflaRx, and ChemoCentryx (more than $10,000 each), research support from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, ChemoCentryx, Forbius, Genetech/Roche, Sanofi-Genzyme, GlaxoSmithKline, and InflaRx, and royalties from *UpToDate*. Dr. Stone has received consulting fees, speaking fees, and/or honoraria from Roche and Genentech (less than $10,000 each). Dr. Sule holds a patent related to the development of the Glucocorticoid Toxicity Index. Dr. Sundel has received royalties from *UpToDate*. Dr. Dua has received consulting fees, speaking fees, and/or honoraria from ChemoCentryx and AbbVie (less than $10,000 each). No other disclosures relevant to this article were reported.

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Submitted for publication September 25, 2020; accepted in revised form April 13, 2021.

trials). For a strong recommendation, the recommended course of action would apply to all or almost all patients. Only a small proportion of clinicians/patients would not want to follow the recommendation. In rare instances, a strong recommendation may be based on very low– to low-certainty evidence. For example, an intervention may be strongly recommended if it is considered low-cost, without harms, and the consequence of not performing the intervention may be catastrophic. An intervention may be strongly recommended against if there is high certainty that the intervention leads to more harm than the comparison with very low or low certainty about its benefit (6).

A *conditional* recommendation is generally supported by lower-quality evidence or a close balance between desirable and undesirable outcomes. For a conditional recommendation, the recommended course of action would apply to the majority of the patients, but the alternative is a reasonable consideration. Conditional recommendations always warrant a shared decision-making approach. We specify conditions under which the alternative may be considered.

In some instances, the committee found that the evidence for a particular PICO question did not support a graded recommendation or did not favor one intervention over the other. However, the Voting Panel believed that the PICO question addressed a commonly encountered clinical question and thus felt that providing guidance for this question was warranted. For these situations, we present "ungraded position statements," which reflect general views of the Voting Panel.

In this evidence-based guideline, we explicitly used the best evidence available and present that in a transparent manner for the clinician reader/user (7). In some instances, this includes randomized trials in which the interventions under consideration are directly compared. The GRADE system rates evidence that comes exclusively from the collective experience of the Voting Panel and Patient Panel members as "very low quality" evidence (5).

For each recommendation, details regarding the PICO questions and the GRADE evidence tables can be found in Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24633/abstract).

RESULTS

For the evidence report, the Literature Review team summarized 127 articles to address 21 PICO questions for PAN.

The following recommendations and ungraded position statements are for systemic PAN and do not apply to isolated cutaneous or HBV-related PAN. Table 1 presents definitions of selected terms used in the recommendations, including the definition of severe and nonsevere disease, as well as dosing ranges for glucocorticoids. Table 2 presents the recommendations with their supporting PICO questions and levels of evidence. Figure 1 provides key recommendations for the treatment for PAN. All but 1 of the recommendations are conditional, primarily due to lack of high-quality evidence (e.g., randomized controlled trials) supporting the recommendation.

Vascular imaging, tissue biopsy, and diagnostic testing

Recommendation: For patients with suspected PAN, we conditionally recommend using abdominal vascular imaging to aid in establishing a diagnosis and determining the extent of disease.

Evidence for the use of routine diagnostic imaging is limited, with no comparative trials available. In single-arm studies that were performed when diagnostic criteria for PAN were not well defined,

Table 1. Definitions of selected terms used in the recommendations for PAN*

Term	Definition
Disease states	
Suspected disease	Clinical signs and/or symptoms suggestive of PAN and not explained by other conditions
Active disease	New, persistent, or worsening clinical signs and/or symptoms attributed to PAN and not related to prior damage
Severe disease	Vasculitis with life- or organ-threatening manifestations (e.g., renal disease, mononeuritis multiplex, muscle disease, mesenteric ischemia, coronary involvement, limb/digit ischemia)
Nonsevere disease	Vasculitis without life- or organ-threatening manifestations (e.g., mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis)
Remission	Absence of clinical signs or symptoms attributed to PAN, on or off immunosuppressive therapy
Refractory disease	Persistent active disease despite an appropriate course of immunosuppressive therapy
Relapse	Recurrence of active disease following a period of remission
Treatments	
IV pulse GCs	IV methylprednisolone 500–1,000 mg/day (adults) or 30 mg/kg/day (children; maximum 1,000 mg/day) or equivalent for 3–5 days
High-dose oral GCs	Prednisone 1 mg/kg/day (adults; generally up to 80 mg/day) or 1–2 mg/kg/day (children; generally up to 60 mg/day) or equivalent
Moderate-dose oral GCs	Prednisone 0.25–0.5 mg/kg/day (adults; generally 10–40 mg/day) or ~0.5 mg/kg/day (children; generally 10–30 mg/day) or equivalent
Low-dose oral GCs	Prednisone ≤10 mg/day (adults) or ≤0.2 mg/kg/day (children; maximum 10 mg/day) or equivalent
Non-GC immunosuppressive therapy	Azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil

* PAN = polyarteritis nodosa; IV = intravenous; GCs = glucocorticoids.

Table 2. Recommendations/statements for the management of PAN*

Recommendation/statement	PICO question informing recommendation and discussion	Level of evidence
Vascular imaging, tissue biopsy, and diagnostic testing		
Recommendation: For patients with suspected PAN, we conditionally recommend using abdominal vascular imaging to aid in establishing a diagnosis and determining the extent of disease.	1	Very low
Recommendation: For patients with a history of severe PAN with abdominal involvement who become clinically asymptomatic, we conditionally recommend follow-up abdominal vascular imaging.	19, 20	Very low
Recommendation: For patients with suspected PAN involving the skin, we conditionally recommend obtaining a deep-skin biopsy specimen (i.e., a biopsy reaching the medium-sized vessels of the dermis) over a superficial skin punch biopsy to aid in establishing a diagnosis.	2	Very low
Recommendation: For patients with suspected PAN and peripheral neuropathy (motor and/or sensory), we conditionally recommend obtaining a combined nerve and muscle biopsy over a nerve biopsy alone to aid in establishing a diagnosis.	3	Very low
Recommendation: For patients with a history of peripheral motor neuropathy secondary to PAN, we conditionally recommend serial neurologic examinations instead of repeated electromyography/nerve conduction studies (e.g., every 6 months) to monitor disease activity.	21	Very low
Treatment of active disease		
Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with IV pulse GCs over high-dose oral GCs.	4	Very low
Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide and high-dose GCs over high-dose GCs alone.	5, 6, 10	Very low to low
Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide and GCs over rituximab and GCs.	5, 6, 10	Very low to low
Recommendation: For patients with newly diagnosed active, severe PAN who are unable to tolerate cyclophosphamide, we conditionally recommend treating with other non-GC immunosuppressive agents and GCs over GCs alone.	8	Very low
Recommendation: For patients with newly diagnosed active, nonsevere PAN, we conditionally recommend treating with non-GC immunosuppressive agents and GCs over GCs alone.	12	Very low
Recommendation: In patients with newly diagnosed active, severe PAN, we conditionally recommend *against* using plasmapheresis combined with cyclophosphamide and GCs over cyclophosphamide and GCs alone.	7, 16	Low
Recommendation: For patients with PAN in remission who are receiving non-GC immunosuppressive therapy, we conditionally recommend discontinuation of non-GC immunosuppressive agents after 18 months over continued (indefinite) treatment.	13	Very low
Ungraded position statement: The optimal duration of GC therapy for PAN (e.g., tapering off by 6 months or longer than 6 months) is not well established, and thus, the duration of therapy should be guided by the patient's clinical condition, values, and preferences.	11	Very low
Treatment of refractory disease		
Recommendation: For patients with severe PAN that is refractory to treatment with GCs and non-GC immunosuppressive agents other than cyclophosphamide, we conditionally recommend switching the non-GC immunosuppressive agent to cyclophosphamide, over increasing GCs alone.	17	Very low
Remission maintenance		
Recommendation: For patients with newly diagnosed PAN who have achieved disease remission with cyclophosphamide, we conditionally recommend transitioning to another non-GC immunosuppressive agent over continuing cyclophosphamide.	9	Very low
Other considerations		
Recommendation: For patients with PAN with nerve and/or muscle involvement, we conditionally recommend physical therapy.	14	Very low
Recommendation: For patients with clinical manifestations of DADA2, we strongly recommend treatment with tumor necrosis inhibitors over GCs alone.	18	Low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for polyarteritis nodosa (PAN), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24633/abstract). IV = intravenous; GCs = glucocorticoids; DADA2 = deficiency of adenosine deaminase 2.

vascular imaging, in tandem with clinical signs and pathology, helped validate the diagnosis (8) and determine disease severity (9). This in turn can influence treatment decisions. Moreover, obtaining vascular imaging at disease onset facilitates identification of new vascular involvement during disease relapse. Vascular imaging may not be warranted if patients present with isolated findings such as mononeuritis multiplex or myopathy, or if there are no clinical features suggestive of abdominal arterial involvement (such as absence of gastrointestinal or genitourinary symptoms, including renovascular hypertension). For children, clinicians should be mindful of minimizing repeated radiation exposure.

Clinicians currently use both conventional catheter-based dye angiography and noninvasive methods such as computed tomography (CT) or magnetic resonance (MR) angiography to diagnose PAN (10–12). Conventional angiography is the current gold standard due to its ability to provide better resolution, but it can be

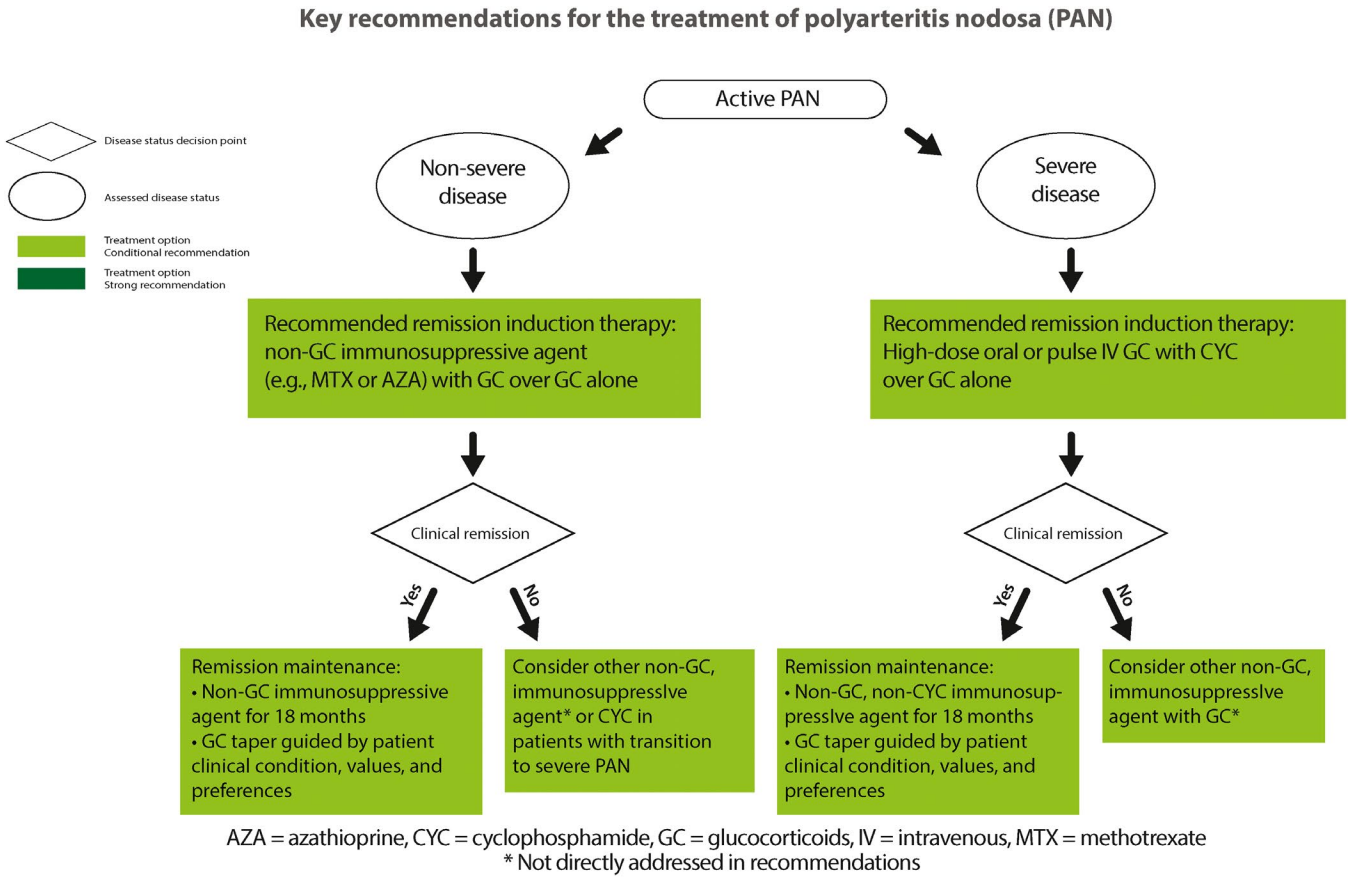
Key recommendations for the treatment of polyarteritis nodosa (PAN)
Disease status decision point
Assessed disease status
Treatment option
Conditional recommendation
Treatment option
Strong recommendation
Active PAN
Non-severe disease
Severe disease
Recommended remission induction therapy: non-GC immunosuppressive agent (e.g., MTX or AZA) with GC over GC alone
Recommended remission induction therapy: High-dose oral or pulse IV GC with CYC over GC alone
Clinical remission
Clinical remission
Yes
No
Yes
No
Remission maintenance:
• Non-GC immunosuppressive agent for 18 months
• GC taper guided by patient clinical condition, values, and preferences
Consider other non-GC, immunosuppresslve agent* or CYC in patients with transition to severe PAN
Remission maintenance:
• Non-GC, non-CYC immunosuppresslve agent for 18 months
• GC taper guided by patient clinical condition, values, and preferences
Consider other non-GC, immunosuppresslve agent with GC*
AZA = azathioprine, CYC = cyclophosphamide, GC = glucocorticoids, IV = intravenous, MTX = methotrexate
* Not directly addressed in recommendations

Figure 1. Key recommendations for the treatment of polyarteritis nodosa.

associated with complications, albeit at a very low rate (13,14). However, the resolution for noninvasive modalities is improving, and CT or MR angiography may provide additional information regarding the vessel wall that conventional angiography does not. Specifically, CT angiography may enable visualization of more of the distal branches of the mesenteric arteries than MR angiography, but MR angiography may be preferred in certain clinical situations (e.g., need to avoid iodinated contrast). In patients with a negative CT or MR angiogram result with a high degree of suspicion for abdominal involvement, it is reasonable to consider conventional angiography.

Recommendation: For patients with a history of severe PAN with abdominal involvement who become clinically asymptomatic, we conditionally recommend follow-up abdominal vascular imaging.

Follow-up imaging permits assessment of disease control and treatment response. In the view of the Voting Panel, follow-up imaging is particularly important when baseline imaging demonstrates aneurysmal disease. The timing of follow-up imaging is dependent, in part, on clinical factors, such as the extent and severity of vascular abnormalities, overall disease course, and response to therapy. However, indefinite routine vascular imaging should be avoided if the abdominal vascular disease is shown to be quiescent.

Recommendation: For patients with suspected PAN involving the skin, we conditionally recommend obtaining a deep-skin biopsy specimen (i.e., a biopsy reaching the medium-sized vessels of the dermis) over a superficial skin punch biopsy to aid in establishing a diagnosis.

Indirect evidence (found in nonrandomized studies or studies in which findings were not primary aims) suggests that evaluation of deeper tissue is more effective at establishing a diagnosis of PAN (15,16), since a deeper-tissue sample is more likely to capture a medium-sized vessel. A deep-skin biopsy can be performed by a dermatologist as a deep (or "double") punch biopsy and does not necessarily require invasive resection. This recommendation had strong support from the Voting Panel but remains conditional due to limited evidence.

Recommendation: For patients with suspected PAN and peripheral neuropathy (motor and/or sensory), we conditionally recommend obtaining a combined nerve and muscle biopsy over a nerve biopsy alone to aid in establishing a diagnosis.

Several studies suggest an increased yield with nerve and concurrent muscle biopsy as opposed to nerve biopsy alone (15–19). However, the biopsy should sample involved tissue and not be performed "blind" (i.e., sampling tissue that does not appear

to be clinically affected). Of note, biopsy of an affected purely sensory nerve (e.g., sural nerve) is favored to avoid motor deficits.

Recommendation: For patients with a history of peripheral motor neuropathy secondary to PAN, we conditionally recommend serial neurologic examinations instead of repeated electromyography/nerve conduction studies (e.g., every 6 months) to monitor disease activity.

This recommendation is based on the opinion of the Voting Panel due to a lack of published evidence addressing the issue. Repeated electromyography in a patient with stable symptoms is *not* recommended due to the invasive nature of this study. However, repeated electromyography/nerve conduction study would be warranted if there were uncertainty as to whether a new (or worsening) process was developing.

Treatment of active disease

Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with intravenous (IV) pulse glucocorticoids over high-dose oral glucocorticoids.

In several single-arm and comparative studies, evaluations of medical therapy were confounded by the use of other medications and did not control for IV pulse or high-dose oral glucocorticoid use (20–22). However, for active and severe disease specifically, patients may benefit from the additional mechanism of action of high-dose pulse glucocorticoids. That is, glucocorticoids may rapidly alter cell membrane and receptor function to promote suppression of inflammation once the glucocorticoid receptor is saturated (23). The Voting Panel noted that this recommendation was focused on patients with active, severe disease. For many patients with disease that is not associated with life-threatening manifestations (such as immediate risk of visceral infarct), oral glucocorticoids would be preferred due to lower overall glucocorticoid burden. For pediatric patients, pulse glucocorticoid therapy in other systemic immune disorders appears to have a favorable side-effect profile and is not more strongly associated with infections or other morbidities compared to oral glucocorticoids (24).

Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide and high-dose glucocorticoids over high-dose glucocorticoids alone.

In newly diagnosed severe PAN, a single observational study and indirect evidence suggest that the use of cyclophosphamide has more benefits than glucocorticoid therapy alone, with no differences seen between oral and IV cyclophosphamide (25,26). Moreover, the use of additional cyclophosphamide cycles may provide a medium-term protection (3 years) against disease relapse, although this benefit wanes by 10 years (21). Use of cyclophosphamide may mitigate glucocorticoid toxicity by decreasing the cumulative steroid dose (27).

Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide and glucocorticoids over rituximab and glucocorticoids.

While case reports have recently raised the question about the efficacy of rituximab use in PAN (28–30), its efficacy in PAN remains uncertain due to the lack of comparative or large single-arm studies in this disease.

Recommendation: For patients with newly diagnosed active, severe PAN who are unable to tolerate cyclophosphamide, we conditionally recommend treating with other nonglucocorticoid immunosuppressive agents and glucocorticoids over glucocorticoids alone.

Indirect evidence (i.e., data obtained from secondary outcomes in prior trials [25,31]) suggests that the combination of nonglucocorticoid immunosuppressive agents, such as azathioprine or methotrexate, with glucocorticoids is superior to glucocorticoids alone. Mycophenolate mofetil has not been well studied in PAN. No direct trials comparing glucocorticoid monotherapy with nonglucocorticoid combination therapy are available. In general, patients with severe PAN should be treated with cyclophosphamide over other immunosuppressive agents (26), but in patients unable to tolerate cyclophosphamide, another agent, such as azathioprine or methotrexate, is recommended over glucocorticoid monotherapy. Use of nonglucocorticoid immunosuppressive therapy may provide a glucocorticoid-sparing effect and minimize glucocorticoid toxicity, which is particularly significant in pediatric populations.

Recommendation: For patients with newly diagnosed active, nonsevere PAN, we conditionally recommend treating with nonglucocorticoid immunosuppressive agents and glucocorticoids over glucocorticoids alone.

In cases of nonsevere disease, a patient's age, clinical condition, and their values and preferences are important factors in assessing treatment. Although some patients achieve disease remission while receiving glucocorticoids alone, a substantial number of patients ultimately require additional nonglucocorticoid therapy, usually azathioprine or methotrexate (20). This recommendation contradicts management recommendations based on the Five-Factor Score (32), in which patients without factors of severe disease can be treated with glucocorticoids alone. We favor the use of nonglucocorticoid therapy in nonsevere disease, since the addition of nonglucocorticoid therapy may minimize glucocorticoid use and subsequent toxicity.

Recommendation: In patients with newly diagnosed active, severe PAN, we conditionally recommend *against* using plasmapheresis combined with cyclophosphamide and glucocorticoids over cyclophosphamide and glucocorticoids alone.

In a single trial conducted in 1995, the use of plasmapheresis in PAN was evaluated, but a distinction between PAN and HBV-associated PAN was not made (33). Confidence intervals in this study were very wide. Thus, evidence supporting the use of plasmapheresis in non–HBV-associated PAN is unavailable and the benefit unclear. Plasmapheresis may be considered in catastrophic cases unresponsive to the recommended aggressive immunosuppressive therapies and may have a role in the management of HBV-related PAN.

Recommendation: For patients with PAN in remission who are receiving nonglucocorticoid immunosuppressive therapy, we conditionally recommend discontinuation of nonglucocorticoid immunosuppressive agents after 18 months over continued (indefinite) treatment.

Evidence for this recommendation is based on a single study that was performed in 1979 (31). Although a significant number of patients with PAN have disease relapse, the majority experience monophasic disease (20). Indefinite treatment may therefore not be needed. Disease needs to be in sustained remission (Table 1) before discontinuing therapy.

Ungraded position statement: The optimal duration of glucocorticoid therapy for PAN (e.g., tapering off by 6 months or longer than 6 months) is not well established, and thus, the duration of therapy should be guided by the patient's clinical condition, values, and preferences.

In PAN, studies to determine the optimal length of time for glucocorticoid use have not been performed. In studies of other types of vasculitis (34), faster tapers led to more flares, which were often not organ-threatening and may have been mild. The Patient Panel preferred a longer taper, as a primary concern was disease control rather than glucocorticoid toxicity. Thus, duration of glucocorticoid use should be influenced by the patient's clinical condition, values, and preferences.

Treatment of refractory disease

Recommendation: For patients with severe PAN that is refractory to treatment with glucocorticoids and nonglucocorticoid immunosuppressive agents other than cyclophosphamide, we conditionally recommend switching the nonglucocorticoid immunosuppressive agent to cyclophosphamide over increasing glucocorticoids alone.

Based on the effectiveness of cyclophosphamide in new-onset severe PAN (26), indirect evidence suggests that cyclophosphamide should be used in patients with PAN that has evolved from a nonsevere presentation to one that is severe and does not adequately respond to other immunosuppressive agents.

Remission maintenance

Recommendation: For patients with newly diagnosed PAN who have achieved disease remission with cyclophosphamide, we conditionally recommend transitioning to another nonglucocorticoid immunosuppressive agent over continuing cyclophosphamide.

Due to its toxicity, cyclophosphamide therapy should not continue indefinitely and should generally be limited to 3–6 months per course (21). Based on the experience in antineutrophil cytoplasmic antibody–associated vasculitis, transitioning to another less toxic agent such as methotrexate or azathioprine is recommended once disease remission has been attained. Given the lack of clinical trials investigating remission maintenance in PAN, this recommendation was based on expert experience.

Other considerations

Recommendation: For patients with PAN with nerve and/or muscle involvement, we conditionally recommend physical therapy.

Indirect evidence for PAN is available for this recommendation from studies in inflammatory myositis. Based on this, we conditionally recommend this intervention due to its potential benefit and minimal risk. Physical therapy may be more beneficial for those with more substantial motor involvement. Patients on the Voting Panel expressed a high degree of enthusiasm for physical therapy as a modality for recovery and rehabilitation, in that they felt they had personally experienced benefit from physical therapy.

Recommendation: For patients with clinical manifestations of deficiency of adenosine deaminase 2 (DADA2), we strongly recommend treatment with tumor necrosis factor inhibitors over glucocorticoids alone.

DADA2 was first described in a series of patients with an early-onset (often childhood) PAN-like vasculitis (35). DADA2 is characterized by recurrent strokes and skin changes and diagnosed using *ADA2* sequencing or ADA2 functional assays, and ADA2 mutations have been identified in patients diagnosed as having systemic PAN (36). Although only 1 case series has been published, the strong signal of benefit of tumor necrosis inhibitors provides evidence that treatment with tumor necrosis inhibitors, instead of conventional immunosuppressive agents such as cyclophosphamide, prevents strokes (35,37). Thus, physicians should consider DADA2 in the setting of a PAN-like syndrome with

strokes, and if confirmed, we strongly recommend use of tumor necrosis factor inhibitors. The Voting Panel voted for a strong recommendation despite the small number of cases, stressing the prevention of severe adverse events.

DISCUSSION

This is the first guideline issued by the ACR, in conjunction with the VF, for the management of systemic PAN. These recommendations constitute a guide to help physicians treat patients with this disease. Because many recommendations are conditional, a patient's clinical condition, values, and preferences should influence the management decisions that are made. These recommendations should not be used by any agency to restrict access to therapy or require that certain therapies be utilized prior to other therapies.

Classic systemic PAN, although rare, remains a disease with a high mortality rate (22). Therefore, recommendations in this guideline indicate that patients with severe disease should be treated with cyclophosphamide and glucocorticoids. However, when patients present with nonsevere disease (i.e., without life- or organ-threatening manifestations such as renal insufficiency and tissue ischemia), use of alternative immunosuppressive agents and a glucocorticoid-sparing regimen is reasonable for remission induction. Use of diagnostic procedures such as angiography, electromyography/nerve conduction studies, and nerve and muscle biopsy is recommended to aid in diagnosis. However, the use of routinely repeated procedures during periods of disease quiescence is discouraged.

PAN has become increasingly rare, and no large clinical trials that focused solely on idiopathic (non–HBV-associated) PAN have been published. In addition, studies of PAN conducted prior to the recognition of microscopic polyangiitis may have included such patients and should be interpreted with caution. Many recommendations were based on expert experience of the Voting Panel and/or trials that were performed several years and, in some cases, decades ago. Strong recommendations will require larger interventional studies but will be challenging to conduct due to the rarity of this disease.

The process of developing these guidelines has brought to our attention other gaps in our understanding of the optimal treatment for PAN. These gaps include the role of longitudinal vascular imaging studies, the comparative effectiveness of nonglucocorticoid immunosuppressive agents, and the lack of biomarkers to inform disease activity or treatment response. Therefore, we encourage continued research in this disease. Future study and specific areas to investigate include the following: 1) determining how informative longitudinal vascular imaging is for assessing disease activity and determining disease prognosis; 2) conducting randomized clinical trials (including comparative efficacy trials) to assess the efficacy of nonglucocorticoid immunosuppressive agents, as well as identifying the optimal dosing, duration, and population that would benefit from these agents; 3) developing novel, targeted, and/or glucocorticoid-sparing therapies with minimal toxicity; and 4) identifying biomarkers to inform assessment of disease activity and prognosis.

In summary, the ACR and the VF present these recommendations to assist physicians in managing PAN, and this guideline can serve as a touchstone for basic principles of management. We hope this guideline will evolve as new research is conducted and new diagnostic and treatment strategies for PAN are identified.

ACKNOWLEDGMENTS

We thank Anne M. Ferris, MBBS, Ora Gewurz-Singer, MD, Rula Hajj-Ali, MD, Eric Matteson, MD, MPH, Robert F. Spiera, MD, Linda Wagner-Weiner, MD, MS, and Kenneth J. Warrington, MD, for serving on the Expert Panel. We thank Antoine G. Sreih, MD, and Gary S. Hoffman, MD, MS, for their contributions during the early phases of this project as members of the Core Team. Dr. Hoffman's participation ended July 2018 due to personal reasons. Dr. Sreih's involvement ended in December 2018 when he became primarily employed by industry, which precluded his continued participation in this project. We thank Joyce Kullman (Vasculitis Foundation) for her assistance with recruitment for the Patient Panel. We thank the patients who (along with authors Kathy A. Full and Omar I. Vitobaldi) participated in the Patient Panel meeting: Jane Ascroft, Scott A. Brunton, Dedra DeMarco, Thomas Fitzpatrick, Jenn Gordon, Maria S. Mckay, Sandra Nye, Stephanie Sakson, and Ben Wilson. We thank Robin Arnold, Catherine E. Najem, MD, MSCE, and Amit Aakash Shah, MD, MPH, for their assistance with the literature review. We thank the ACR staff, including Ms Regina Parker, for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, and Ms Robin Lane for assistance in manuscript preparation. We thank Ms Janet Waters for help in developing the literature search strategy and performing the initial literature search, and Ms Janet Joyce for performing the update searches.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Chung and Gorelik had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Chung, Gorelik, Langford, Maz, Abril, Guyatt, Archer, Full, Grayson, Merkel, Seo, Stone, Sule, Sundel, Vitobaldi, Turner, Mustafa.

Acquisition of data. Chung, Gorelik, Langford, Maz, Abril, Full, Imundo, Kim, Merkel, Stone, Vitobaldi, Byram, Dua, Husainat, James, Kalot, Lin, Springer, Turgunbaev, Villa-Forte, Turner, Mustafa.

Analysis and interpretation of data. Chung, Gorelik, Langford, Maz, Abril, Archer, Conn, Full, Grayson, Ibarra, Imundo, Kim, Merkel, Rhee, Seo, Stone, Vitobaldi, Warner, Byram, Dua, Husainat, Kalot, Lin, Springer, Turgunbaev, Mustafa.

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ARTHRITIS & RHEUMATISM
Vol. 64, No. 4, April 2012, pp 943–954
DOI 10.1002/art.34356
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Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and wileyonlinelibrary.com

2012 Provisional Classification Criteria for Polymyalgia Rheumatica

A European League Against Rheumatism/American College of Rheumatology Collaborative Initiative

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This criteria set has been approved by the European League Against Rheumatism (EULAR) Executive Committee and the American College of Rheumatology (ACR) Board of Directors as Provisional. This signifies that the criteria set has been quantitatively validated using patient data, but it has not undergone validation based on an external data set. All EULAR/ACR-approved criteria sets are expected to undergo intermittent updates.

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The objective of this study was to develop European League Against Rheumatism/American College of Rheumatology classification criteria for polymyalgia rheumatica (PMR). Candidate criteria were evaluated in a 6-month prospective cohort study of 125 patients with new-onset PMR and 169 non-PMR comparison

This article is published simultaneously in the April 2012 issue of *Annals of the Rheumatic Diseases*.

Supported by the American College of Rheumatology, the European League Against Rheumatism, and the Mayo Foundation. Additional support was provided by the Biobanque de Picardie, Amiens, France. Drs. Espígol-Frigolé and Cid's work was supported by the Ministerio de Ciencia y Tecnologia, Spain (SAF 08/04328).

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subjects with conditions mimicking PMR. A scoring algorithm was developed based on morning stiffness >45 minutes (2 points), hip pain/limited range of motion (1 point), absence of rheumatoid factor and/or anti–citrullinated protein antibody (2 points), and absence of peripheral joint pain (1 point). A score ≥4 had 68% sensitivity and 78% specificity for discriminating all comparison subjects from PMR. The specificity was higher (88%) for discriminating shoulder conditions from PMR and lower (65%) for discriminating RA from PMR. Adding ultrasound, a score ≥5 had increased sensitivity to 66% and specificity to 81%. According to these provisional classification criteria, patients ≥50 years old presenting with bilateral shoulder pain, not better explained by an alternative pathology, can be classified as having PMR in the presence of morning stiffness >45 minutes, elevated C-reactive protein and/or erythrocyte sedimentation rate, and new hip pain. These criteria are not meant for diagnostic purposes.

Polymyalgia rheumatica (PMR) is a common inflammatory rheumatic disease of older individuals and a common indication for long-term corticosteroid therapy (1–3). PMR is also subject to wide variations of clinical practice, due to the considerable uncertainty related to diagnosis, course, and management in primary and secondary care (4–7). There is no diagnostic laboratory test, inflammatory markers are not specific, and clinicians often turn to the corticosteroid response as a "test of treatment" to establish the diagnosis (1,2,8).

Difficulties in diagnosing and classifying patients with PMR are inherent in its definitions (9,10). The proximal pain and stiffness syndrome can occur at presentation in many other rheumatologic inflammatory illnesses in older people (1,2,7,9). Approximately half of patients diagnosed with PMR may have distal manifestations such as peripheral arthritis, hand swelling with pitting edema, and carpal tunnel syndrome (1,2,7,11). Polymyalgic presentation is common in late-onset rheumatoid arthritis (RA) and spondylarthritis and is also associated with giant cell arteritis in 10–30% of cases (1,2). Heterogeneity in the disease course, uncertainty regarding disease assessment parameters, and evolution of alternative diagnoses on followup complicate the management of PMR (9,12–15). For the above reasons a safe and specific approach preferring a relative underdiagnosis to an overdiagnosis is needed in PMR (9,11).

Uniform responsiveness to low doses of corticosteroids has been assumed to be a cardinal feature of PMR. However, there is little hard evidence to substantiate this assertion. A previous report showed that 3 weeks after starting prednisolone 15 mg a day only 55% showed a complete response to therapy (10). This also emphasizes that clinical trials of novel effective agents are needed in PMR.

The lack of standardized classification criteria has been a major factor hampering the development of rational therapeutic approaches (12,16,17) and causing difficulties in evaluating patients in clinical studies. In response to a European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) initiative, a criteria development work group convened in 2005.

A systematic literature review, a 3-phase hybrid consensus process, and a wider survey were undertaken to identify candidate criteria items (18). The first stage

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Dr. Dasgupta has received consulting fees, speaking fees, and/or honoraria from Mundipharma and Novartis UK (less than $10,000 each). Dr. Schirmer has received consulting fees, speaking fees, and/or honoraria from Abbott and MSD (less than $10,000 each). Dr. Bachta has received consulting fees, speaking fees, and/or honoraria from Abbott Poland, MSD Poland, and Pfizer Poland (less than $10,000 each). Dr. Dejaco has received consulting fees, speaking fees, and/or honoraria from MSD, Roche, Merck, Bristol-Myers Squibb, Pfizer, and Abbott (less than $10,000 each). Dr. Martínez-Taboada has received consulting fees, speaking fees, and/or honoraria from Pfizer, MSD, and Roche (less than $10,000 each). Dr. Aydin has received honoraria from Abbott (less than $10,000). Dr. Wakefield has received consulting fees, speaking fees, and/or honoraria from Abbott (less than $10,000). Dr. Michet has received consulting fees, speaking fees, and/or honoraria from UpToDate (less than $10,000). Dr. Matteson has received consulting fees from Novartis (less than $10,000) and has served as an unpaid advisory board member for Horizon Pharma.

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Submitted for publication June 21, 2011; accepted in revised form October 31, 2011.

consisted of a meeting of 27 international experts who anonymously rated 68 potential criteria identified through literature review. In the second round the experts were provided with the results of the first round and re-rated the criteria items. In the third round the wider acceptance of the chosen criteria (>50% support) was evaluated using a survey of 111 rheumatologists and 53 nonrheumatologists in North America and western Europe.

In round 3, over 70% of respondents agreed on the importance of 7 core criteria (all achieving 100% support in round 2). These were aged 50 years or older, symptom duration 2 weeks or longer, bilateral shoulder and/or pelvic girdle aching, duration of morning stiffness more than 45 minutes, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), and rapid corticosteroid response. More than 70% agreed on assessing pain and limitation of shoulder (84%) and/or hip (76%) motion, but agreement was low for peripheral signs (e.g., carpal tunnel syndrome, tenosynovitis, peripheral arthritis).

The group reached consensus on the need for a prospective cohort study to evaluate the disease course from presentation in patients included on the basis of proximal pain and stiffness, with evaluations over a 6-month period while receiving a standardized corticosteroid treatment regimen (7,18–25). The group also agreed to assess musculoskeletal ultrasound as part of the PMR classification criteria. In this paper, we present the results from this prospective study and propose new classification criteria for PMR.

STUDY DESIGN AND METHODS

Consensus decisions about study design. A priori, the work group decided that a specific approach should be adopted for classifying newly presenting patients with bilateral shoulder pain as PMR (18). The group agreed on the following:

1. Patients presenting with polymyalgic syndrome should have stepwise evaluation on the basis of inclusion and exclusion criteria, response to a standardized corticosteroid challenge, and followup confirmation. The criteria items would be agreed-upon clinical features and laboratory investigations.

2. The need to standardize response to corticosteroid therapy in PMR. Because the goal of classification criteria is to identify patients for enrollment into clinical trials before any treatment, the response to corticosteroid therapy should be used in verifying the classification of a patient as having PMR, although it should not be used as a classification criterion. Because scientific evidence is poor as to what constitutes such a response it was agreed (>75% agreement) this response would be defined as >75% global response in clinical and laboratory parameters within 7 days of corticosteroid challenge with 15 mg oral prednisone or prednisolone and subsequent resolution of inflammatory indices (18).

3. That a prospective study would be needed to evaluate the disease course from presentation in patients included on the basis of the mandatory "core" criteria of proximal pain and stiffness. New-onset bilateral shoulder pain was selected as the main eligibility criterion as the percentage of PMR presenting with hip pain without shoulder pain was very small (<5%), and that as hip girdle pain is due to a wide range of conditions, it would require the enrollment of an impracticably large number of comparator patient groups (18). The study would evaluate at prespecified intervals symptoms, examination, investigations, and their evolution with standardized corticosteroid treatment in a prospective cohort of patients with new-onset bilateral shoulder pain (comparing the PMR case cohort with the comparator cohort of mimicking conditions) over a 6-month period.

4. Musculoskeletal ultrasound should be evaluated in a substudy as a feasible mode of investigation of possible PMR. A secondary objective of this substudy would be the evaluation of clinical and patient-based outcomes in PMR over a 6-month period (26,27).

Study population. The study was a prospective cohort study that included a cohort of patients with new-onset PMR and a comparison cohort of non-PMR patients with various conditions mimicking PMR. Study subjects were recruited from 21 community-based and academic rheumatology clinics in 10 European countries and the USA. Inclusion criteria for PMR patients were age 50 years or older, new-onset bilateral shoulder pain, and no corticosteroid treatment (for any condition) within 12 weeks before study entry, fulfilling all the inclusion and exclusion criteria defined in our previous report and in accordance with the judgment of the participating investigator that the patient had PMR (18). Every effort was made to choose patients across the spectrum of disease severity. Corticosteroid treatment for PMR patients was initiated according to a predefined treatment protocol starting with 15 mg a day oral prednisone for weeks 1 and 2, 12.5 mg a day for weeks 3 and 4, 10 mg a day for weeks 6–11, 10 mg/7.5 mg every other day for weeks 12–15, 7.5 mg a day for weeks 16–25, and tapering according to treatment response from week 26 onward. The gold standard for the pre-steroid diagnosis of PMR was established as above at presentation and when the diagnosis was maintained without an alternative diagnosis at week 26 of followup.

The non-PMR comparison cohort included conditions representative of the types that need to be distinguished from PMR, in both primary and secondary care. Inclusion criteria for the non-PMR comparison cohort were age 50 years or older, new-onset bilateral shoulder pain, and a diagnosis of either inflammatory or noninflammatory conditions, including new-onset RA, connective tissue diseases, various shoulder conditions (e.g., bilateral rotator cuff syndrome and/or adhesive capsulitis, rotator cuff tear, glenohumeral osteoarthritis), fibromyalgia, generalized osteoarthritis, and others. Patients known to have the condition for >12 weeks before the baseline evaluation (except fibromyalgia and chronic pain) were not eligible for inclusion. PMR patients with clinical suspicion of giant cell arteritis were included as part of the comparison cohort because these patients required different corticosteroid doses. Patients in the comparison cohort were included on the

basis of clinician diagnosis and not on formal criteria. No guidelines were provided for treatment of the conditions in the comparison cohort.

Ethics board approval was obtained at all participating institutions before initiation of the study, and all participants gave written informed consent before enrollment.

Followup and data collection. PMR patients were evaluated at baseline, and at 1, 4, 12, and 26 weeks. At each followup visit, clinical evaluation included response to corticosteroid therapy and opinion on the emergence of alternative diagnoses. Patients not considered as having PMR at any time were evaluated and treated according to accepted clinical practice. They were excluded from the PMR cohort and included in the non-PMR comparison cohort. Patients in the comparison cohort were evaluated at baseline and at 26 weeks.

Data were collected using standardized data collection forms and questionnaires translated into national languages. Data collection included the candidate inclusion/exclusion criteria items for classification of PMR, physical examination, and assessment of corticosteroid response. Criteria items were age 50 years or older, symptom duration 2 weeks or more, bilateral shoulder and/or pelvic girdle aching, recent weight loss >2 kg, duration of morning stiffness >45 minutes, elevated ESR, elevated CRP, and rapid response of symptoms to corticosteroids (>75% global response within 1 week to prednisolone/prednisone 15–20 mg a day). Pain was assessed using a horizontal 100-mm visual analog scale (VAS) in 4 separate locations (shoulder, pelvic, neck, and overall) with 0 indicating no pain and 100 indicating worst pain. Morning stiffness (in the past 24 hours) was assessed in minutes; functional status and quality of life were assessed by the modified Health Assessment Questionnaire (M-HAQ) and Short Form 36. A 100-mm VAS was also used for recording global well-being measures (patient and physician global) and fatigue. Physical examination included the presence or absence of tenderness, pain on movement, and limitation of the shoulders and hips. Aspects of corticosteroid therapy including dose, therapeutic response, and change in dose and therapy discontinuation were documented.

Data regarding laboratory measures (including ESR, CRP, rheumatoid factor [RF], and anti–citrullinated protein antibody [ACPA]) were obtained from clinically ordered tests performed at each study center. As the laboratory assays used at each center varied, test results were classified as normal/abnormal using the reference ranges from each center (see Supplementary Table 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131). Both PMR and non-PMR subjects underwent ultrasound evaluation of shoulders and hips at baseline and at 26 weeks. Evaluations were made according to EULAR guidelines (28) to assess for features previously reported to be associated with PMR, including bicipital tenosynovitis, subacromial and subdeltoid bursitis, trochanteric bursitis, and glenohumeral and hip effusion. A rheumatologist or radiologist experienced in musculoskeletal ultrasound performed the ultrasound examination using linear probes with the frequency range 6–10 MHz for shoulders and linear or curved array probes with the frequency range 5–8 MHz for hips.

Statistical analysis. Descriptive statistics (means, percentages, etc.) were used to summarize the candidate criteria data. Demographics (age and gender) and candidate criteria were compared between PMR and comparison subjects using chi-square and rank sum tests. Several statistical approaches were considered in order to develop a scoring algorithm for PMR and to assess the proposed classification criteria in patients judged by expert clinician investigators to have PMR 26 weeks after enrollment (29).

First, logistic regression models to distinguish PMR patients from all comparison subjects and each subset of comparison subjects were examined. The C statistic, a measure of concordance analogous to the area under the receiver operating characteristic curve, was used to assess the ability of each individual criterion to distinguish between PMR and comparison subjects. The C statistic ranges from 0.5 to 1, with 0.5 indicating a criterion that provides no information. The sensitivity, specificity, and the positive and negative likelihood ratios were also examined.

Second, exploratory factor analysis was used to examine the interdependencies between the candidate criteria (30). Maximum-likelihood factor analysis with varimax rotation was used. Maximum-likelihood tests were used to examine goodness of fit (e.g., to determine the number of factors). This method is thought to be superior to the eigenvalue >1 or Cattell's scree plot method for selecting the number of factors (30). For each factor, variables with factor loadings >0.5 were examined and found to represent a similar domain. This technique allowed a reduction of the number of variables, as one variable from each factor was examined in multivariable logistic regression models. In addition, to avoid discarding a relevant domain as identified by expert consensus, a few of the variables with factor loading between 0.4 and 0.5 were also considered in the multivariable models.

Classification trees including the variables determined by the factor analysis were also considered, but were not found to be optimal for distinguishing PMR from comparison subjects (31,32). An integer scoring algorithm was defined based on the odds ratios in the final multivariable logistic regression model. Performance characteristics (sensitivity, specificity, etc.) of this scoring algorithm were assessed. In addition, the utility of ultrasound assessments for classifying PMR patients was examined using factor analysis and adding potential ultrasound criteria to the scoring algorithm. Odds ratios for clinical criteria varied somewhat in the scoring algorithm that included ultrasound criteria. Scoring weights based on both models were considered and found to perform similarly, so a common set of scoring weights was used for the clinical items in both algorithms in order to ease comparison and application of the criteria.

Finally, gradient boosting regression tree models, which are a machine learning technique, were examined to determine whether a better prediction could be achieved using a more complex algorithm (33).

RESULTS

At baseline, 128 patients were recruited into the PMR cohort and 184 patients were recruited into the non-PMR comparison cohort. During followup, 10 PMR patients were reclassified as not having PMR and moved into the non-PMR cohort. Similarly, 8 non-PMR com-

Table 1. Distribution of candidate criteria for 125 PMR patients and 169 comparison subjects*

	PMR (n = 125)	Comparison subjects (n = 169)	*P*	RA (n = 49)	*P*	Shoulder conditions (n = 52)†	*P*
Age, mean ± SD years	71.5 ± 8.4	67.0 ± 9.6	<0.001	68.6 ± 10.0	0.06	67.0 ± 10.6	0.017
Female sex	72 (58)	112 (66)	0.13	28 (57)	0.96	35 (67)	0.23
Duration of symptoms ≥2 weeks	121 (97)	163 (96)	0.87	47 (96)	0.77	51 (98)	0.64
Duration of symptoms, mean ± SD weeks	10.0 ± 7.2	14.4 ± 19.1	0.17	13.8 ± 16.1	0.62	12.9 ± 11.8	0.21
Bilateral shoulder aching	124 (99)	162 (96)	0.08	46 (94)	0.035	50 (96)	0.15
Bilateral pelvic girdle (hip) aching	91 (73)	90 (53)	0.001	28 (57)	0.046	21 (40)	<0.001
Neck aching	71 (57)	92 (54)	0.69	29 (59)	0.78	27 (52)	0.55
Morning stiffness duration >45 minutes‡	92 (77)	68 (43)	<0.001	33 (69)	0.25	10 (20)	<0.001
Morning stiffness duration, median (IQR) minutes	120 (60, 240)	30 (5, 120)	<0.001	60 (30, 180)	0.11	10 (0, 30)	<0.001
Weight loss of >2 kg	45 (36)	40 (24)	0.021	16 (33)	0.68	4 (8)	<0.001
Shoulder pain or limited range of motion	121 (97)	158 (93)	0.20	47 (96)	0.77	49 (94)	0.42
Hip pain or limited range of motion	71 (57)	59 (35)	<0.001	15 (31)	0.002	12 (23)	<0.001
Shoulder tenderness	96 (77)	126 (75)	0.66	40 (82)	0.49	34 (65)	0.12
Hip tenderness	59 (47)	47 (28)	0.001	12 (24)	0.006	9 (17)	<0.001
Carpal tunnel syndrome	19 (15)	27 (16)	0.90	11 (22)	0.28	8 (15)	0.99
Peripheral synovitis (distal swelling, tenosynovitis, or arthritis)‡	48 (39)	78 (46)	0.20	41 (84)	<0.001	11 (21)	0.024
Other joint pain‡	63 (51)	109 (66)	0.011	40 (85)	<0.001	29 (57)	0.50
Abnormal CRP and/or ESR‡	116 (96)	99 (63)	<0.001	41 (85)	0.017	18 (41)	<0.001
Presence of RF and/or ACPA‡	11 (10)	37 (25)	0.004	19 (41)	<0.001	5 (12)	0.79
Abnormal serum protein electrophoresis‡	43 (52)	32 (35)	0.027	9 (36)	0.17	9 (35)	0.13
M-HAQ, mean ± SD	1.2 ± 0.6	0.8 ± 0.6	<0.001	1.1 ± 0.7	0.32	0.5 ± 0.6	<0.001

* Values are number (percentage) unless specified. Percentages for laboratory results are the number of abnormal test results divided by the number of patients tested. PMR = polymyalgia rheumatica; RA = rheumatoid arthritis; IQR = interquartile range; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; M-HAQ = modified Health Assessment Questionnaire.
† Bilateral rotator cuff syndrome and/or adhesive capsulitis, rotator cuff tear, glenohumeral osteoarthritis.
‡ Data not available on all subjects.

parison cohort patients were reclassified as having PMR and moved into the PMR cohort. In addition, 7 patients (1 PMR and 6 non-PMR) were excluded due to missing information, and 2 non-PMR subjects with age <50 years and 9 non-PMR subjects with no shoulder pain were also excluded. Therefore, the final analysis was based on 125 PMR and 169 non-PMR subjects.

The diagnoses of the 169 non-PMR subjects (see Supplementary Table 2, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131) were new-onset RA (49 [29%]), new-onset other seronegative arthritis (20 [12%]), new-onset connective tissue diseases or vasculitis (9 [5%]), shoulder conditions (52 [31%]), chronic pain (26 [15%]), infection (5 [3%]), previously undiagnosed malignancy (4 [2%]), and 2 each of endocrinopathy and neurologic disorders.

The distribution of the candidate classification criteria for the 125 PMR patients and 169 non-PMR comparison subjects (all, RA only, and shoulder condition only) is displayed in Table 1. Criteria items present in >80% of the PMR subjects were ≥2 weeks duration of symptoms, bilateral shoulder pain, and elevated CRP and/or ESR. Relevant clinical features that best discriminated RA from PMR were peripheral synovitis, the presence of RF and/or ACPA, and hip pain/limited range of motion. Features best discriminating shoulder conditions from PMR were hip pain/limited range of motion, morning stiffness, and elevated CRP and/or ESR.

Development of a scoring algorithm. Table 2 shows the results of univariate logistic regression models to distinguish PMR from all comparison subjects, RA only, and shoulder conditions only. Criteria items related to hip involvement (pain, tenderness, limited movement) had significant ability to discriminate PMR from all comparison subjects, RA, and shoulder conditions based on the C statistic. Early morning stiffness, M-HAQ, weight loss, and raised laboratory markers of inflammation distinguished PMR from comparison subjects, particularly those with shoulder conditions. The presence of ACPA and/or RF, peripheral synovitis, and joint pains had significant ability (with high C statistic) to distinguish PMR from RA. In addition, the odds

Table 2. Univariate logistic regression models to distinguish subjects with PMR from comparison subjects*

Variable	PMR vs. all comparison subjects		PMR vs. RA		PMR vs. shoulder conditions†	
	Odds ratio (95% CI)	C	Odds ratio (95% CI)	C	Odds ratio (95% CI)	C
Duration of symptoms ≥2 weeks	1.1 (0.3–4.0)	0.50	1.3 (0.2–7.3)	0.50	0.6 (0.1–5.4)	0.51
Shoulder pain or limited range of motion	2.1 (0.7–6.8)	0.52	1.3 (0.2–7.3)	0.50	1.9 (0.4–8.6)	0.51
Shoulder tenderness	1.1 (0.7–1.9)	0.51	0.7 (0.3–1.7)	0.52	1.8 (0.9–3.6)	0.56
Hip pain or limited range of motion	2.5 (1.5–3.9)	0.61	3.0 (1.5–6.0)	0.63	4.4 (2.1–9.1)	0.67
Hip tenderness	2.3 (1.4–3.8)	0.60	2.8 (1.3–5.8)	0.61	4.3 (1.9–9.5)	0.65
Neck aching	1.1 (0.7–1.8)	0.51	0.9 (0.5–1.8)	0.51	1.2 (0.6–2.3)	0.52
Morning stiffness duration >45 minutes	4.5 (2.6–7.7)	0.67	1.5 (0.7–3.3)	0.54	13.6 (6.0–31)	0.79
Weight loss >2 kg	1.8 (1.1–3.0)	0.56	1.2 (0.6–2.4)	0.52	6.8 (2.3–19.9)	0.64
Carpal tunnel syndrome	1.0 (0.5–1.8)	0.50	0.6 (0.3–1.5)	0.54	–	–
Peripheral synovitis (distal swelling, tenosynovitis, or arthritis)	0.7 (0.5–1.2)	0.54	0.1 (0.08–0.3)	0.72	2.4 (1.1–5.0)	0.59
Other joint pain	0.5 (0.3–0.9)	0.57	0.2 (0.1–0.4)	0.67	0.8 (0.4–1.5)	0.53
Abnormal CRP and/or ESR	13.8 (5.3–36)	0.67	4.0 (1.2–13)	0.55	33.5 (11–98)	0.78
Presence of RF and/or ACPA	0.4 (0.2–0.7)	0.57	0.2 (0.07–0.4)	0.66	0.9 (0.3–2.6)	0.51
Abnormal serum protein electrophoresis	2.0 (1.1–3.6)	0.58	1.9 (0.8–4.8)	0.58	2.0 (0.8–5.1)	0.59
M-HAQ (per 1-unit increase)	2.3 (1.6–3.4)	0.66	1.3 (0.7–2.2)	0.55	6.7 (3.2–14)	0.78

* PMR = polymyalgia rheumatica; 95% CI = 95% confidence interval; RA = rheumatoid arthritis; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; M-HAQ = modified Health Assessment Questionnaire.
† Bilateral rotator cuff syndrome and/or adhesive capsulitis, rotator cuff tear, glenohumeral osteoarthritis.

ratios for abnormal CRP and/or ESR were particularly high. This resulted because only 5 PMR patients did not have abnormal CRP and/or ESR, perhaps reflecting that the diagnosis of PMR is less certain in the presence of normal CRP and ESR. Therefore, abnormal CRP or ESR would be included as a required criterion in the scoring algorithm for PMR. Similarly, as all subjects in the study were required to have shoulder pain, this was also included as a required criterion for PMR.

Factor analysis revealed that 4 factors were sufficient to represent all the criteria (see Supplementary Table 3, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131). These 4 factors were hip pain/tenderness, peripheral synovitis or other joint pain, morning stiffness, and shoulder tenderness. Note that duration of symptoms, neck aching, carpal tunnel syndrome, weight loss, presence of RF/ACPA, and M-HAQ did not play a prominent role in any of the factors.

Next, multivariable logistic regression models were used to determine the importance of each criterion when assessed simultaneously (Table 3). Three models

Table 3. Multivariable logistic regression models*

Criterion	Model based on factors		Model based on factors without shoulder tenderness plus presence of RF/ACPA		Model based on factors plus presence of RF/ACPA and M-HAQ	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Hip pain or limited range of motion	2.7 (1.5–4.8)	0.001	2.1 (1.1–4.0)	0.019	1.6 (0.8–3.2)	0.16
Other joint pain	0.4 (0.2–0.6)	<0.001	0.4 (0.2–0.7)	0.002	0.3 (0.1–0.6)	<0.001
Morning stiffness duration >45 minutes	5.2 (2.9–9.4)	<0.001	6.2 (3.2–11.8)	<0.001	4.8 (2.4–9.6)	<0.001
Shoulder tenderness	0.9 (0.5–1.8)	0.80				
Presence of RF or ACPA			0.3 (0.1–0.8)	0.009	0.3 (0.1–0.8)	0.013
M-HAQ, per 1-unit increase					2.4 (1.4–4.2)	0.002
Likelihood ratio test for additional terms			$P < 0.001$		$P < 0.001$	
C statistic	79%		81%		81%	

* 95% CI = 95% confidence interval; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; M-HAQ = modified Health Assessment Questionnaire.

Table 4. Scoring algorithm with and without optional ultrasound criteria—required criteria: age ≥50 years, bilateral shoulder aching, and abnormal CRP and/or ESR*

Criteria	Clinical criteria (without ultrasound)†		Criteria including ultrasound‡	
	Odds ratio (95% CI)	Points	Odds ratio (95% CI)	Points
Morning stiffness duration >45 minutes	6.2 (3.2–11.8)	2	5.0 (2.8–9.1)	2
Hip pain or limited range of motion	2.1 (1.1–4.0)	1	1.4 (0.8–2.6)	1
Absence of RF or ACPA	3.0 (1.3–6.8)	2	5.2 (2.1–12.6)	2
Absence of other joint pain	2.7 (1.4–5.0)	1	2.2 (1.3–4.0)	1
Ultrasound criteria				
At least 1 shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least 1 hip with synovitis and/or trochanteric bursitis			2.6 (1.3–5.3)	1§
Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis			2.1 (1.2–3.7)	1¶

* CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; 95% CI = 95% confidence interval; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody.
† The optimal cut point is 4. A patient with a score of 4 or more is categorized as having polymyalgia rheumatica (PMR).
‡ The optimal cut point is 5. A patient with a score of 5 or more is categorized as having PMR.
§ $P = 0.008$.
¶ $P = 0.009$.

were considered: 1) including the 4 factors identified in factor analysis; 2) removing shoulder tenderness and adding presence of RF/ACPA; and 3) subsequently adding M-HAQ. While the subsequent additions appeared to be significant, they also negatively impacted the hip pain criteria. The utility of the inclusion of M-HAQ was questionable, as hip pain was easier to assess than M-HAQ in a clinical setting. Therefore, the second model, which included hip pain, other joint pain, morning stiffness, and abnormal RF/ACPA, was deemed the best multivariable model.

Additional analyses were performed using classification trees and assessing combinations of criteria. Classification trees were examined using 3 sets of potential variables: 1) the 4 identified factors; 2) adding presence of RF/ACPA; and 3) subsequently adding M-HAQ. The resulting trees were deemed inadequate. For example, the second tree, which was fit using the same 5 variables that were included in our scoring algorithm, had a sensitivity of 66% and specificity of 66%. This specificity was lower than the scoring algorithm developed from the logistic models. In addition, this tree only included morning stiffness and absence of RF and/or ACPA, so it was inadequate because it excluded other domains deemed necessary for content validity. Content validity requires that the set of criteria identified is comprehensive. This was the case in all 3 trees. Therefore, classification trees were deemed to have poorer performance and content validity than the logistic regression models.

A scoring algorithm was developed (Table 4) based on the multivariable logistic regression model presented in Table 3 and included morning stiffness for >45 minutes (2 points), hip pain/limited range of motion (1 point), absence of RF and/or ACPA (2 points), and the absence of peripheral joint pain (1 point). The score was evaluated using all PMR subjects (including the 5 with normal CRP/ESR) and all comparison subjects. This was done to account properly for the influence of CRP/ESR on the performance of the scoring algorithm. A score of 4 or greater had 68% sensitivity and 78% specificity for discriminating all comparison subjects from PMR. The specificity was higher (88%) for discriminating shoulder conditions from PMR and lower (65%) for discriminating RA from PMR. The C statistic for the scoring algorithm was 81%. A total of 40 PMR patients (32%) and 38 comparison subjects (22%) were incorrectly classified. The positive predictive value was 69% and the negative predictive value was 77%. Supplementary Table 4 (http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131) shows the sensitivity and specificity for all possible cut points of the scoring algorithm.

Finally, gradient boosting regression tree models, which are a model averaging technique, were examined to determine whether a better prediction could be

Table 5. Ultrasound findings in 120 patients with PMR, 154 comparison subjects (including 46 with RA and 47 with shoulder conditions), and 21 subjects without shoulder conditions*

	PMR (n = 120)	Comparison subjects (n = 154)	RA (n = 46)	Shoulder conditions (n = 47)	Subjects without shoulder conditions (n = 21)
At least 1 shoulder with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	83	70†	78	62†	19†
Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	59	43†	65	26†	0†
At least 1 shoulder with subdeltoid bursitis or biceps tenosynovitis	82	63†	72	53†	19†
Both shoulders with subdeltoid bursitis or biceps tenosynovitis	57	35†	52	21†	0†
At least 1 hip with synovitis or trochanteric bursitis	38	23‡	30	18‡	0†
Both hips with synovitis or trochanteric bursitis	19	8†	9	4‡	0‡
At least 1 shoulder and 1 hip with findings as above	33	16†	17‡	11†	0†
Both shoulders and both hips with findings as above	12	7	6	2‡	0

* Values are percents. RA = rheumatoid arthritis.
† $P < 0.01$ compared with polymyalgia rheumatica (PMR).
‡ $P < 0.05$ compared with PMR.

achieved using a more complex algorithm. The resulting C statistic from the gradient boosting model was 80%, which was quite comparable to the results for our scoring algorithm. This indicated that we will not be able to make better predictions from these data with another modeling approach.

Ultrasound findings. Ultrasound was performed in 120 PMR subjects, 154 of the comparison subjects (including 46 with RA and 47 with shoulder conditions), and 21 additional controls (not included in our study cohorts) who did not have shoulder conditions. Patients with PMR were more likely to have abnormal ultrasound findings in the shoulder (particularly subdeltoid bursitis and biceps tenosynovitis), and somewhat more likely to have abnormal findings in the hips than comparison subjects as a group (Table 5). PMR could not be distinguished from RA on the basis of ultrasound, but could be distinguished from non-RA shoulder conditions and subjects without shoulder conditions.

Assessing the utility of ultrasound in classifying PMR. Factor analysis (see Supplementary Table 5, http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131) revealed several strong factors potentially useful for classifying patients with PMR from the ultrasound data. The inclusion of ultrasound findings in the scoring algorithm resulted in improving the C statistic to 82%. A score of 5 or greater had 66% sensitivity and 81% specificity for discriminating all comparison subjects from PMR. The specificity was higher (89%) for discriminating shoulder conditions from PMR and lower (70%) for discriminating RA from PMR. A total of 41 PMR patients (34%) and 30 comparison subjects (19%) were incorrectly classified. The positive predictive value was 72% and the negative predictive value was 75%. Therefore, ultrasound findings were useful in discriminating PMR from shoulder conditions, but less so in discriminating PMR from RA. Table 4 also shows the scoring algorithm including the ultrasound criteria. Supplementary Table 4 (http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131) shows the sensitivity and specificity for all possible cut points of the scoring algorithm.

Response to corticosteroids in PMR. Complete corticosteroid response at 4 weeks was seen in 71% of patients and the response was sustained in 78% of responders at 26 weeks. As expected by the plan for tapering of the corticosteroids, the median prednisone dose decreased from 15 mg at baseline to 5 mg at 26 weeks. Response to treatment (percentage improvement in global pain VAS at weeks 4 and 26) was highly correlated with percentage improvement in other VAS measures (correlation >0.5 and $P < 0.001$ at weeks 4 and 26), but was not correlated with percentage change in corticosteroid dose ($P = 0.20$ at week 4 and $P = 0.47$ at week 26). There was no association between the points obtained on either scoring algorithm and the response to corticosteroids at 4 weeks (Spearman correlation coefficient 0.09, $P = 0.38$ for the scoring algorithm including ultrasound) and 26 weeks (data not shown), indicating that corticosteroid response cannot be used as part of PMR classification.

We also reevaluated our risk score model for the scoring algorithm using only the PMR subjects who responded to corticosteroids. When the final risk score

model was recomputed using only the subset of subjects with PMR who responded to corticosteroids (and all of the comparison subjects), the odds ratios for each of the criteria remained essentially unchanged. In addition, the specificity was identical and the sensitivity increased by an insignificant amount (0.5%).

Blinded reevaluation of selected PMR patients and non-PMR controls. The reevaluation exercise showed that most candidate criteria items performed well in discriminating PMR patients from controls. However, a third of the sample of PMR patients/comparison subjects was difficult to classify. The high C statistic levels associated with the corticosteroid response and posttreatment CRP and ESR suggested that the uncertainty originated from the pivotal role of corticosteroids in the investigator assessment, in deciding whether a patient does or does not have PMR. It raises questions such as whether PMR always responds adequately to corticosteroids and whether polymyalgic RF-positive disease without peripheral synovitis can occur (see Supplementary Appendix [http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131)] for details).

Table 6. PMR classification criteria scoring algorithm—required criteria: age ≥50 years, bilateral shoulder aching, and abnormal CRP and/or ESR*

	Points without US (0–6)	Points with US (0–8)†
Morning stiffness duration >45 minutes	2	2
Hip pain or limited range of motion	1	1
Absence of RF or ACPA	2	2
Absence of other joint involvement	1	1
At least 1 shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least 1 hip with synovitis and/or trochanteric bursitis	NA	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	NA	1

* A score of 4 or more is categorized as polymyalgia rheumatica (PMR) in the algorithm without ultrasound (US) and a score of 5 or more is categorized as PMR in the algorithm with US. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; NA = not applicable.
† Optional ultrasound criteria.

DISCUSSION

This is the first international multicenter prospective study examining consensus-based candidate classification criteria for PMR proposed by an international work group. Findings indicate that patients 50 years of age or older presenting with new bilateral shoulder pain (not better explained by an alternative diagnosis) and elevated CRP and/or ESR can be classified as having PMR in the presence of morning stiffness of >45 minutes and new hip involvement (pain, tenderness, limited movement). The absence of peripheral synovitis or of positive RA serology increases the likelihood of PMR. While recognizing that RF particularly may be present in patients with PMR, the absence of RF serology is useful in distinguishing PMR from RA in older patients for classification purposes (18,34). Ultrasound findings of bilateral shoulder abnormalities (subacromial bursitis/bicipital tenosynovitis/glenohumeral effusion) or abnormalities in 1 shoulder and hip (hip effusion, trochanteric bursitis) may significantly improve the specificity of the clinical criteria. These criteria are not meant for diagnostic purposes and have not been tested as diagnostic criteria.

Newer concepts of PMR are revealed by this and other recent studies—heterogeneity at presentation and course, lack of uniform responsiveness to low-dose steroids, and overlap with inflammatory arthritis. However, we feel that at present these classification criteria provide a basic framework for developing clinical trials of novel therapies in PMR.

How should the PMR classification criteria be applied? The target population will be patients aged 50 years or older presenting with new-onset (<12 weeks) bilateral shoulder pain and abnormal acute-phase response. The criteria may only be applied to those patients in whom the symptoms are not better explained by an alternative diagnosis. Mimicking conditions include the inflammatory and noninflammatory conditions studied as comparators in this report.

Four clinical and laboratory criteria along with optional ultrasound criteria (Tables 4 and 6) can be applied to eligible patients to identify patients with PMR suitable for low-dose corticosteroid therapy. The scoring scale is 0–6 (without ultrasound) and 0–8 (with ultrasound). In the absence of competing diagnoses, a score of 4 or greater (without ultrasound), or 5 or greater (with ultrasound) is indicative of PMR. Patients with a score of less than 4 (based on clinical plus laboratory criteria) cannot be considered to have PMR. Ultrasound improves the specificity of PMR diagnosis, and shows particularly good performance in differentiating PMR from noninflammatory conditions and thus is a recommended investigation for PMR.

Classification criteria for PMR should be useful for identifying patients appropriate for enrollment into clinical trials of novel medications for the treatment of PMR, and studying long-term outcomes in more homogeneous patient cohorts. Our analyses indicate that even typical PMR patients at presentation may vary in their response to low-dose corticosteroid therapy, indicating that corticosteroid response is not reliable as a classification feature for PMR. This is similar to other rheumatic diseases such as RA, in which phenotypically similar patients may exhibit different responses to disease-modifying antirheumatic drugs.

Strengths and limitations. The strengths of the study relate to harnessing international effort to address a disease area subject to wide variation of practice, to develop agreement on the definition of what may or may not be treated as PMR and what needs further evaluation.

Our study methodology satisfies the ACR guidelines for the development of classification criteria for rheumatic diseases (35). The consensus-based candidate criteria were generated by a multispecialty international group whose views were supported by the results of a wide trans-Atlantic survey. The work group suggested a prospective study designed to separate PMR patients from comparison subjects in patients included on a single eligibility criterion (new bilateral shoulder pain in subjects $\geq$50 years).

This ensured an inception cohort longitudinal observational design wherein the PMR cohort could be compared with the comparison cohort at similar chronological time points of disease. All PMR patients were evaluated before treatment with corticosteroids, were treated with a standard corticosteroid schedule, and assessed at predetermined time points. Our study is in keeping with the EULAR/ACR goal of developing rheumatic disease classification criteria as opposed to diagnostic criteria. We focused on subjects with new-onset/incident disease, and a 6-month longitudinal followup allowed an accurate evaluation of the disease course and diagnoses. Previous criteria for PMR were developed using cross-sectional comparisons. Only 2 of the previous criteria were developed through an evaluative process (20,36). Neither had a definition of the "gold standard" diagnosis other than the physician considered the patient to have "unequivocal" PMR.

Another strength of our proposed classification criteria is the imaging component. Musculoskeletal ultrasound has promise due to widespread availability, feasibility, and good research evidence (18). The PMR work group standardized the examination of shoulders and hips by ultrasound for the purposes of the current study (37). Our findings indicate that ultrasound evaluation of hips and shoulders adds significantly to the evaluation of the polymyalgic syndrome. The lack of a "gold standard" and the challenge of circularity were addressed through a blinded multirater reevaluation exercise in selected cases and comparison subjects (see Supplementary Appendix [http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131)]). Most of the candidate criteria items performed well. The misclassification of several subjects reflects the difficulty in discriminating PMR from other inflammatory conditions such as RA. This uncertainty originates from the pivotal role of (and circular reasoning related to using) the corticosteroid response in deciding whether a patient does or does not have PMR. Although the proposed scoring algorithm has high specificity for identifying PMR patients, it is nevertheless unable to predict the subsequent corticosteroid response, suggesting heterogeneity of disease course and treatment response. This has also been reported previously (10,38).

While we were able to scrutinize the basis for PMR diagnosis, no formal criteria were required for diagnosis of the comparison conditions. This is a limitation of the study. However, the study was led in all centers by experienced rheumatologists with major clinical and research interest in PMR and related conditions. We did not include hip pain without shoulder pain as an eligibility criterion for reasons discussed in the Methods section. Funding constraints limited the followup duration to only 6 months. We were also limited by lack of funding for the central measurement of laboratory data. Values of ESR, CRP, RF, and ACPA were based on local laboratory assays. Our study approach reflects a pragmatic view, which perhaps lends wider applicability to the results of the study.

Our classification algorithm had a C statistic of 81%, which exceeds the threshold of 80% that is conventionally considered to be useful in clinical decision-making. However, we suggest that the criteria are regarded as provisional at this point, awaiting validation in a separate cohort.

In conclusion, patients aged 50 years or older presenting with bilateral shoulder pain and elevated CRP and/or ESR can be classified as having PMR in the presence of morning stiffness for more than 45 minutes, and new hip pain in the absence of peripheral synovitis or positive RA serology. Using ultrasound, a score of 5 or greater had 66% sensitivity and 81% specificity for discriminating all comparison subjects from PMR. In our view, this approach can now be used to test eligibility

for trials with newer therapies in PMR. A number of future research questions are highlighted, including: 1) Should PMR be considered as a part of the spectrum of late-onset inflammatory arthritis? 2) Can polymyalgic disease without peripheral synovitis occur in RF-positive disease? 3) Can we diagnose PMR in patients with normal acute-phase response? 4) What is the role of the early introduction of disease-modifying antirheumatic drugs in PMR?

We have collected and stored blood samples from both the case and the comparator groups in the study. We hope to develop research proposals using these biospecimens to test several candidate biomarkers in PMR. These proposals will also examine the acute-phase response: whether stratification of the response and differential levels of acute-phase reactants and cytokines may function as additional classification criteria items.

ACKNOWLEDGMENTS

The investigators would like to acknowledge EULAR, ACR, the Mayo Foundation, and the Biobanque de Picardie in Amiens, France, for material and intellectual support of this project. The investigators also wish to recognize the individual and uncompensated efforts of the staff at each participating institution, without which this study could not have been completed.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Dasgupta and Matteson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Dasgupta, Cimmino, Maradit Kremers, W. Schmidt, Bachta, Dejaco, Duftner, Balint, Z. Schmidt, Del Amo, Cid, Nordborg, Luqmani, Abril, Marcus, Gonter, Carter, Crowson, Matteson.

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Arthritis & Rheumatology
Vol. 0, No. 0, Month 2022, pp 1–9
DOI 10.1002/art.42324
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Empowering Rheumatology Professionals

2022 American College of Rheumatology/EULAR Classification Criteria for Takayasu Arteritis

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the EULAR Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

The ACR is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.

Objective. To develop and validate new classification criteria for Takayasu arteritis (TAK).

Methods. Patients with vasculitis or comparator diseases were recruited into an international cohort. The study proceeded in 6 phases: 1) identification of candidate criteria items, 2) collection of candidate items present at diagnosis, 3) expert panel review of cases, 4) data-driven reduction of candidate items, 5) derivation of a points-based classification score in a development data set, and 6) validation in an independent data set.

Results. The development data set consisted of 316 cases of TAK and 323 comparators. The validation data set consisted of an additional 146 cases of TAK and 127 comparators. Age ≤60 years at diagnosis and imaging evidence of large-vessel vasculitis were absolute requirements to classify a patient as having TAK. The final criteria items and weights were as follows: female sex (+1), angina (+2), limb claudication (+2), arterial bruit (+2), reduced upper extremity pulse (+2), reduced pulse or tenderness of a carotid artery (+2), blood pressure difference between arms of ≥20 mm Hg (+1), number of affected arterial territories (+1 to +3), paired artery involvement (+1), and abdominal aorta plus renal or mesenteric involvement (+3). A patient could be classified as having TAK with a cumulative score of ≥5 points. When these criteria were tested in the validation data set, the model area under the curve was 0.97 (95% confidence interval [95% CI] 0.94–0.99) with a sensitivity of 93.8% (95% CI 88.6–97.1%) and specificity of 99.2% (95% CI 96.7–100.0%).

Conclusion. The 2022 American College of Rheumatology/EULAR classification criteria for TAK are now validated for use in research.

This article is published simultaneously in *Annals of the Rheumatic Diseases*.

The Diagnostic and Classification Criteria in Vasculitis (DCVAS) study, which included the development of this classification criteria, was funded by grants from the American College of Rheumatology (ACR), EULAR, the Vasculitis Foundation, and the University of Pennsylvania Vasculitis Center. This study was also supported by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH.

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INTRODUCTION

Takayasu arteritis (TAK) is one of the major forms of large-vessel vasculitis (LVV) (1). TAK is a chronic disease defined by granulomatous inflammation affecting the aorta and its primary branches. Complications from vascular damage can result in substantial morbidity including stroke, myocardial infarction, mesenteric ischemia, and limb claudication.

Unlike diagnostic criteria, the purpose of classification criteria is to ensure that a homogenous population is selected for inclusion into clinical trials and other research studies (2). In 1990, the American College of Rheumatology (ACR) endorsed classification criteria for TAK (3). These criteria were developed using data from only 63 patients with TAK and have never been independently validated. Additionally, these criteria were derived using data from patients exclusively from North America without representation from Europe or Asia, where clinical patterns of disease may differ (4), limiting the generalizability of results. Given these constraints, the 1990 ACR criteria for TAK no longer satisfy accepted current standards (5) for classification criteria development, and updated criteria are warranted. Further highlighting a need for uniform, revised criteria in TAK is the use of divergent eligibility criteria to define study populations in 2 recent randomized clinical trials conducted in North America and Japan, making comparisons between the trial findings difficult (6,7).

Advancements in imaging techniques and the ongoing adoption of noninvasive vascular imaging approaches in clinical practice have broadened understanding of the clinical heterogeneity in LVV (8). Disease of the extracranial arteries is increasingly recognized in patients with giant cell arteritis (GCA), making the distinction between TAK and GCA more challenging (9). Age is typically used as a primary classifier to differentiate between TAK and GCA; however, specific age thresholds to define each disease have not been standardized. Therefore, in addition to incorporating data from a larger patient population from a wider geographic spectrum, the updated TAK classification criteria should reflect modern clinical practice, including current imaging techniques, and also define specific age thresholds.

This article outlines the development and validation of the new ACR/EULAR-endorsed classification criteria for TAK.

METHODS

An international Steering Committee comprising clinician investigators with expertise in vasculitis, statisticians, and data managers was established to oversee the overall development of classification criteria for primary vasculitis (10). A detailed and complete description of the methods involved in the development and validation of the classification criteria for TAK is located in Supplementary Appendix 1 (http://onlinelibrary.wiley.com/doi/10.1002/art.42324). Briefly, the Steering Committee implemented a 6-stage plan using data-driven and consensus methodology to develop the following criteria.

Stage 1: generation of candidate classification items for the systemic vasculitides. Candidate classification items were generated by expert opinion and reviewed by a group of vasculitis experts across a range of specialties using nominal group technique.

Stage 2: Diagnostic and Classification Criteria for Vasculitis (DCVAS) prospective observational study. A prospective, international, multisite observational study was conducted (see Appendix A for study investigators and sites). Ethical approval was obtained from local ethics committees. Consecutive patients representing the full spectrum of vasculitides were recruited from academic and community practices. Patients were included if they were 18 years or older and had a diagnosis of vasculitis or a condition that mimics vasculitis (e.g., infection, malignancy, atherosclerosis). Patients with TAK could only be enrolled within 5 years of diagnosis. Only data present at diagnosis were used to develop the classification criteria.

Stage 3: expert review to derive a gold standard–defined set of cases of LVV. Experts in vasculitis from a wide range of geographic locations and specialties (see Appendix A) reviewed all submitted cases of vasculitis and a random selection of vasculitis mimics. Each reviewer was asked to review ~50 submitted cases to confirm the diagnosis and to specify the degree of certainty of their diagnosis as follows: very certain, moderately certain, uncertain, or very uncertain. Only cases agreed upon with at least moderate certainty by 2 reviewers were retained for further analysis.

Stage 4: refinement of candidate items specifically for LVV. The Steering Committee conducted a data-driven process to reduce the number of candidate items of relevance to cases

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.42324&file=art42324-sup-0001-Disclosureform.pdf.

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Submitted for publication February 14, 2022; accepted in revised form July 30, 2022.

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and comparators for LVV. Density plots were assessed to study age distribution at diagnosis and symptom onset for TAK and GCA. Absolute age requirements versus incorporation of age as a candidate criteria item were considered. Items related to the vascular physical examination, vascular imaging, arterial biopsy, and laboratory values were combined or eliminated based on consensus review. Items were selected for exclusion if they had a prevalence of <5% within the data set, and/or they were not clinically relevant for classification criteria (e.g., related to infection, malignancy, or demography). Low-frequency items of clinical importance could be combined, when appropriate. Patterns of vascular imaging findings detected by vascular ultrasound, angiography, or positron emission tomography were defined by K-means clustering (11).

Stage 5: derivation of the final classification criteria for TAK. The DCVAS data set was split into development (70%) and validation (30%) sets. Comparisons were performed between cases of TAK and a randomly selected comparator group in the following proportions: GCA, 33.6%; other vasculitides that mimic GCA and TAK (isolated aortitis, primary central nervous system vasculitis, polyarteritis nodosa, Behçet's disease, and other LVV), 33.1%; a comparator mimic of LVV (e.g., headache syndrome or atherosclerosis), 33.3%. Least absolute shrinkage and selection operator (lasso) logistic regression was used to identify predictors from the data set and create a parsimonious model including only the most important predictors. The final items in the model were formulated into a clinical risk-scoring tool, with each factor assigned a weight based on its respective regression coefficient. A threshold that best balanced sensitivity and specificity was identified for classification.

Stage 6: validation of the final classification criteria for TAK. Performance of the new criteria was validated in an independent set of cases and comparators. Performance of the final classification criteria was examined in specific subsets of patients with TAK using data from the combined development and validation sets, to maximize sample sizes for the subgroups. Patients were studied according to different intervals of age at diagnosis to determine if the criteria performed well across the age spectrum of TAK. Performance characteristics of the new criteria were also tested in patients recruited into the DCVAS study from different regions of the world where prevalence of TAK and clinical assessment approaches may differ. Comparison was made between the measurement properties of the new 2022 ACR/EULAR classification criteria for TAK and the 1990 ACR classification criteria.

RESULTS

Generation of candidate classification items for the systemic vasculitides. The Steering Committee identified >1,000 candidate items for the DCVAS Case Report Form (Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/art.42324).

DCVAS prospective observational study. Between January 2011 and December 2017, the DCVAS study recruited 6,991 participants from 136 sites in 32 countries. Information on the DCVAS sites, investigators, and study participants is listed in Supplementary Appendices 3, 4, and 5 (http://onlinelibrary.wiley.com/doi/10.1002/art.42324).

Expert review methodology to derive a gold standard–defined final set of cases of LVV. The LVV expert panel review process included 56 experts who reviewed vignettes derived from the Case Report Forms for 2,131 cases submitted with a diagnosis of LVV (1,608 [75.5% of Case Report Forms]), another type of vasculitis (118 [5.5% of Case Report Forms]), or a mimic of vasculitis (405 [19.0% of Case Report Forms]). Characteristics and the list of expert reviewers are shown in Supplementary Appendices 6 and 7 (http://onlinelibrary.wiley.com/doi/10.1002/art.42324). A sample vignette and the LVV expert panel review flow chart are shown in Supplementary Appendices 8 and 9. A total of 1,695 cases (80%) passed the main LVV process. An additional 373 cases of LVV and comparators, confirmed during a previous review process to derive the classification criteria for antineutrophil cytoplasmic antibody–associated vasculitis, were also included. In total, after both review processes, 2,068 cases were available for the stages 4 and 5 analyses.

The submitting physician diagnosis of TAK was confirmed in 500 of 610 cases (82.0%) after both expert panel reviews. The reasons for exclusion were diagnosis of TAK categorized as "uncertain" or "very uncertain" during panel review (n = 95) or change in diagnosis during panel review to another type of vasculitis (e.g., GCA, isolated aortitis, LVV that could not be subtyped) (n = 10) or to a comparator disease (n = 5). An additional 9 patients who were not initially diagnosed as having TAK by the submitting physician were diagnosed as having TAK after panel review and DCVAS Steering Committee member adjudication. Per Steering Committee consensus, imaging evidence of LVV was considered an absolute requirement to classify TAK. Of 509 cases confirmed by expert panel review, 47 patients with TAK did not have documented disease according to a vascular imaging study and were excluded from further analysis, leaving a total of 462 patients with TAK for subsequent analysis.

Refinement of candidate items specifically for TAK. Patients with TAK were diagnosed in the following age groups: 18–39 years (n = 355; 77%); 40–60 years (n = 104; 23%); and >60 years (n = 3; <1%) (see Supplementary Appendix 10 for the distribution of "age at diagnosis" in patients with LVV, and the similar distribution of "age at symptom onset," http://onlinelibrary.wiley.com/doi/10.1002/art.42324). Therefore, an age

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of ≤60 years at diagnosis was considered an absolute requirement to classify a patient as having TAK.

Prevalence of arterial damage (stenosis, occlusion, or aneurysm) was greater in TAK compared to GCA in the following 9 arterial territories: thoracic aorta, abdominal aorta, left and right carotid, left and right subclavian, mesenteric, and left and right renal arteries (Supplementary Appendix 11, http://onlinelibrary.wiley.com/doi/10.1002/art.42324). Therefore, a composite variable representing the number of affected arteries was created based upon luminal damage in those 9 territories. As previously reported, cluster analyses identified vascular damage in the abdominal aorta and the renal or mesenteric arteries as a specific imaging pattern for TAK in the DCVAS cohort (11); thus, this arterial pattern was tested as a potential classifier of TAK (Supplementary Appendix 12, http://onlinelibrary.wiley.com/doi/10.1002/art.42324). Symmetric disease in branch arteries (carotid, subclavian, and renal arteries) was seen in 30.3% patients with TAK compared to 2.7% of the comparators ($P < 0.01$) and, therefore, was included as a potential classifier. A systolic blood pressure difference of ≥20 mm Hg between upper extremities optimized specificity to differentiate TAK from other forms of LVV.

Following a data-driven and expert consensus process, 72 items from the DCVAS Case Report Form were retained for lasso regression analysis, including 32 demographic and clinical items, 14 laboratory items (including values of C-reactive protein level and erythrocyte sedimentation rate, each divided into 5 categories), 14 imaging items (13 composite), 11 vascular examination items (5 composite, and upper extremity blood pressure divided into 6 categories), and 1 arterial biopsy item (Supplementary Appendix 13, http://onlinelibrary.wiley.com/doi/10.1002/art.42324). Criteria for TAK and GCA were independently derived from this common set of 72 items.

Derivation of the final classification criteria for TAK. Table 1 lists the demographic and disease features of the 462 patients with TAK and 450 comparators used to develop and validate the criteria, of which 316 patients with TAK and 323 comparators were in the development data set and 146 patients with TAK and 127 comparators were in the validation data set. The patients with TAK were recruited from Asia (n = 298), Europe (n = 130), North America (n = 28), Africa (n = 3), and Oceania (n = 3). Clinical diagnoses assigned to patients in the comparator group are detailed in Supplementary Appendix 14 (http://onlinelibrary.wiley.com/doi/10.1002/art.42324).

Lasso logistic regression analysis using all 72 items resulted in a model of 9 independent items (Supplementary Appendix 15B, http://onlinelibrary.wiley.com/doi/10.1002/art.42324). Weighting of individual criterion was based on logistic regression fitted to the 9 selected predictors. The number of affected arterial territories functioned as an almost perfect classifier (Supplementary Appendix 16B) and was thus also included in the final model, with criterion weighting determined by consensus of the Steering Committee (Supplementary Appendix 17B).

Validation of the final classification criteria for TAK. Using a cutoff of ≥5 in total risk score in the validation data set (see Supplementary Appendix 18B for cutoff points), the sensitivity was

Table 1. Demographic and disease features of the patients with Takayasu arteritis and the comparators*

	TAK (n = 462)	Comparators (n = 450)†	*P*
Age, mean ± SD years	32.3 ± 10.4	58.6 ± 18.0	<0.001
Female sex	391 (84.6)	246 (54.7)	<0.001
Clinical features			
Angina	56 (12.1)	7 (1.6)	<0.001
Arm claudication	233 (50.4)	11 (2.4)	<0.001
Leg claudication	88 (19.0)	17 (3.8)	<0.001
Vascular examination findings			
Arterial bruit	263 (56.9)	32 (7.1)	<0.001
Reduced or absent pulse in upper extremity	309 (66.9)	16 (3.6)	<0.001
Carotid artery with reduced pulse or tenderness	171 (37.0)	16 (3.6)	<0.001
Difference in systolic blood pressure ≥20 mm Hg between arms	190 (41.1)	16 (3.6)	<0.001
Imaging findings			
1 affected arterial territory	76 (16.5)	36 (8.0)	<0.001
2 affected arterial territories	114 (24.7)	12 (2.7)	<0.001
≥3 affected arterial territories	89 (19.2)	5 (1.1)	<0.001
Vasculitis affecting paired branch arteries	140 (30.3)	12 (2.7)	<0.001
Abdominal aorta involvement with renal or mesenteric artery involvement	83 (18.0)	5 (1.1)	<0.001

* Except where indicated otherwise, values are the number (%).
† Diagnoses of comparators for the classification criteria for Takayasu arteritis (TAK) included giant cell arteritis (n = 151), Behçet's disease (n = 80), polyarteritis nodosa (n = 39), clinically isolated aortitis (n = 12), primary central nervous system vasculitis (n = 11), large-vessel vasculitis (LVV) that could not be subtyped (n = 7), and other diseases that mimic LVV (n = 150).

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93.8% (95% confidence interval [95% CI] 88.6–97.1%), and the specificity was 99.2% (95% CI 96.7–100.0%). The area under the curve for the model was 0.97 (95% CI 0.94–0.99) (Supplementary Appendix 19B, http://onlinelibrary.wiley.com/doi/10.1002/art.42324). The final classification criteria for TAK are shown in Figure 1 (for the slide presentation versions, see Supplementary Figure 1, http://onlinelibrary.wiley.com/doi/10.1002/art.42324).

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EULAR

CLASSIFICATION CRITERIA FOR **TAKAYASU ARTERITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify the patient as having Takayasu arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

ABSOLUTE REQUIREMENTS

Age ≤ 60 years at time of diagnosis	
Evidence of vasculitis on imaging[1]	

ADDITIONAL CLINICAL CRITERIA

Female sex	+1
Angina or ischemic cardiac pain	+2
Arm or leg claudication	+2
Vascular bruit[2]	+2
Reduced pulse in upper extremity[3]	+2
Carotid artery abnormality[4]	+2
Systolic blood pressure difference in arms ≥ 20 mm Hg	+1

ADDITIONAL IMAGING CRITERIA

Number of affected arterial territories (select one)[5]	
One arterial territory	+1
Two arterial territories	+2
Three or more arterial territories	+3
Symmetric involvement of paired arteries[6]	+1
Abdominal aorta involvement with renal or mesenteric involvement[7]	+3

Sum the scores for 10 items, if present. A score of ≥ 5 points is needed for the classification of TAKAYASU ARTERITIS.

1. Evidence of vasculitis in the aorta or branch arteries must be confirmed by vascular imaging (e.g., computed tomographic/catheter-based/magnetic resonance angiography, ultrasound, positron emission tomography).
2. Bruit detected by auscultation of a large artery, including the aorta, carotid, subclavian, axillary, brachial, renal, or iliofemoral arteries.
3. Reduction or absence of pulse by physical examination of the axillary, brachial, or radial arteries.
4. Reduction or absence of pulse of the carotid artery or tenderness of the carotid artery.
5. Number of arterial territories with luminal damage (e.g., stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography from the following nine territories: thoracic aorta, abdominal aorta, mesenteric, left or right carotid, left or right subclavian, left or right renal arteries.
6. Bilateral luminal damage (stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography in any of the following paired vascular territories: carotid, subclavian, or renal arteries.
7. Luminal damage (stenosis, occlusion, aneurysm) detected by angiography or ultrasonography involving the abdominal aorta and either the renal or mesenteric arteries.

Figure 1. The final 2022 American College of Rheumatology/EULAR Classification Criteria for Takayasu arteritis.

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Table 2. Performance characteristics of the 2022 ACR/EULAR classification criteria for Takayasu arteritis*

Patient subset	Total no. patients (no. TAK patients)	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Development data set	639 (316)	89.9 (86.0–93.0)	96.6 (94.0–98.3)	0.93 (0.91–0.95)
Validation data set	273 (146)	93.8 (88.6–97.1)	99.2 (96.7–100.0)	0.97 (0.94–0.99)
Age intervals				
18–39 years	437 (351)	94.0 (91.0–96.3)	97.7 (91.9–99.7)	0.96 (0.94–0.98)
40–60 years	226 (104)	83.7 (75.1–90.2)	91.8 (85.4–96.0)	0.88 (0.83–0.92)
World regions				
North America	127 (28)	85.7 (67.3–96.0)	92.9 (86.0–97.1)	0.89 (0.82–0.96)
Europe	422 (130)	91.5 (85.4–95.7)	94.9 (91.7–97.1)	0.93 (0.90–0.96)
North America/Europe combined	549 (158)	90.5 (84.8–94.6)	94.4 (91.6–96.4)	0.92 (0.90–0.95)
Asia	357 (298)	92.0 (88.3–94.8)	93.2 (83.5–98.1)	0.94 (0.89–0.96)

* Performance characteristics for the age and regional subsets were reported using data from the combined development and validation data sets to maximize sample size. ACR = American College of Rheumatology; TAK = Takayasu arteritis; 95% CI = 95% confidence interval; AUC = area under the curve.

The performance characteristics of the criteria in different subsets of patients with TAK are shown in Table 2 and Supplementary Appendix 20B. For patients who were diagnosed between 18 and 39 years of age, the sensitivity of the criteria was 94.0% (95% CI 91.0–96.3%), and the specificity was 97.7% (95% CI 91.9–99.7%). For patients who were diagnosed between 40 and 60 years of age, the sensitivity of the criteria was 83.7% (95% CI 75.1–90.2%), and the specificity was 91.8% (95% CI 85.4–96.0%). Because age restrictions are absolute requirements for the 2022 ACR/EULAR classification criteria for TAK (≤60 years at diagnosis) and GCA (≥50 years at diagnosis), patients with LVV between the ages of 50 and 60 years are potentially eligible to fulfill criteria for TAK and GCA. Of the 26 patients with TAK diagnosed between the ages of 50 and 60 years, 23 (88.5%) were classified correctly as having TAK, 1 (3.9%) was incorrectly classified as having GCA, and 1 (3.9%) fulfilled criteria for both TAK and GCA (Supplementary Appendix 21, http://onlinelibrary.wiley.com/doi/10.1002/art.42324). The criteria performed well in both Asia (sensitivity 92.0%, specificity 93.2%) and Europe/North America (sensitivity 90.5%, specificity 94.4%).

When the 1990 ACR classification criteria for TAK were applied to the DCVAS validation data set, the criteria performed poorly due to low sensitivity (84.3% [95% CI 77.3–89.7%]) but retained excellent specificity (99.2% [95% CI 95.7–100.0%]). In particular, the 1990 criteria had poor sensitivity for patients who were diagnosed as having TAK between 40 and 60 years of age (62.5% [95% CI 52.5–71.8%]).

DISCUSSION

Presented here are the final 2022 ACR/EULAR TAK classification criteria. A 6-stage approach was used, underpinned by data from the multinational, prospective DCVAS study and informed by expert review and consensus at each stage. The comparator group for developing and validating the criteria were other vasculitides and conditions that mimic TAK, where discrimination from TAK is difficult but important. In the validation data set, the new criteria had a sensitivity of 93.8% (95% CI 88.6–97.1%) and a specificity of 99.2% (95% CI 96.7–100.0%). These are the official final values that should be quoted when referring to the criteria. The sensitivity and specificity values calculated in the development data set were very similar, providing reassurance that the statistical methods avoided overfitting of models. Calculations of sensitivity and specificity for patient subgroups were made in the combined development and validation data sets to maximize sample sizes for the subgroups. Reassuringly, the new criteria for TAK have excellent sensitivity and specificity across different regions of the world. The criteria also incorporate modern imaging techniques, which are useful both to diagnose LVV and to differentiate among different types of vasculitis. The criteria were designed to have face and content validity for use in clinical trials and other research studies.

These criteria are validated and intended for the purpose of *classification* of vasculitis and are not appropriate for use to establish a *diagnosis* of vasculitis (2). The aim of the classification criteria is to differentiate cases of TAK from similar types of vasculitis in research settings (5). Therefore, *the criteria should only be applied when a diagnosis of large- or medium-vessel vasculitis has been made and all potential "vasculitis mimics" have been excluded*. For example, the criteria were not developed to differentiate patients with TAK from patients with atherosclerosis or noninflammatory genetic diseases that damage the large arteries. The 1990 ACR classification criteria for vasculitis perform poorly when used for diagnosis (i.e., when used to differentiate between cases of vasculitis versus mimics without vasculitis), and it is expected that the 2022 criteria would also perform poorly if used inappropriately as diagnostic criteria (12).

The 2022 ACR/EULAR TAK classification criteria reflect the collaborative effort of the international vasculitis community to delineate the salient clinical features that differentiate TAK from

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other forms of vasculitis, most notably GCA. The final criteria include 10 clinical items that are routinely assessed during clinical evaluation of patients with TAK. The criteria highlight the importance of clinical symptoms, vascular physical examination, and vascular imaging as important disease classifiers. Features of TAK may differ in patients from different parts of the world (13). The 2022 ACR/EULAR TAK classification criteria retained excellent performance characteristics when tested in patients from different regions, including Asia where the disease is most prevalent (14). While TAK is often considered a disease of the young, 25% of the patients with TAK in the DCVAS cohort were older than 40 years at the time of diagnosis. Therefore, an age at diagnosis of ≤60 years, rather than a lower age threshold, was set as an absolute requirement for disease classification. The 2022 ACR/EULAR TAK classification criteria performed well when applied to patients ages 18–60 years and outperformed the 1990 ACR Classification Criteria for TAK in the subset of patients diagnosed as having TAK ages 40–60 years.

There are several strengths of the new 2022 ACR/EULAR TAK classification criteria. The criteria were developed by a large group of international experts in systemic vasculitis, with guidance from the ACR regarding modern methods of classification criteria development. The criteria represent several important methodologic advancements compared to the original 1990 ACR classification criteria for TAK. First, expert review rather than submitting physician diagnosis was used as the diagnostic reference standard to minimize investigator bias. Second, while the 1990 ACR criteria were entirely derived using data from 63 North American patients with TAK and not validated in a separate data set, the new criteria were developed in 316 patients with TAK and validated in an independent data set which contained an additional 146 patients with TAK from an international cohort. Third, unlike the 1990 ACR criteria, the new ACR/EULAR TAK criteria are weighted to reflect the relative importance of specific items (e.g., number of affected arterial territories). Finally, when both criteria sets were tested within the DCVAS cohort, the performance characteristics of the 2022 ACR/EULAR TAK criteria outperformed the 1990 ACR criteria.

There are some study limitations to consider. Acquisition of clinical and imaging data among patients with LVV and comparators was not standardized (e.g., not all pulses were recorded by the investigators; patients with suspected diagnosis of TAK rarely underwent investigation of the cranial arteries; temporal artery biopsy was not performed in all patients with suspected GCA). However, this limitation reflects the existing differences in how these diseases are assessed in routine clinical practice. Most patients were recruited from Europe, Asia, and North America, with fewer patients from Africa and Oceania. The performance characteristics of the criteria should be further tested in populations that were underrepresented in the DCVAS cohort and may have different clinical presentations of TAK. These criteria were developed using data collected from adult patients with vasculitis and should be tested in children with TAK (15).

The 2022 ACR/EULAR classification criteria for TAK are the product of a rigorous methodologic process that utilized an extensive data set generated by the work of a remarkable international group of collaborators. These criteria have been endorsed by the ACR and EULAR and are now ready for use in research.

ACKNOWLEDGMENTS

We acknowledge the patients and clinicians who provided data to the DCVAS project.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Merkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Vaccinations

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Arthritis Care & Research
Vol. 0, No. 0, Month 2023, pp 1–16
DOI 10.1002/acr.25045
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2022 American College of Rheumatology Guideline for Vaccinations in Patients With Rheumatic and Musculoskeletal Diseases

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Objective. To provide evidence-based recommendations on the use of vaccinations in children and adults with rheumatic and musculoskeletal diseases (RMDs).

Methods. This guideline follows American College of Rheumatology (ACR) policy guiding management of conflicts of interest and disclosures and the ACR guideline development process, which includes the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. It also adheres to the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria. A core leadership team consisting of adult and pediatric rheumatologists and a guideline methodologist drafted clinical population, intervention, comparator, outcomes (PICO) questions. A review team performed a systematic literature review for the PICO questions, graded the quality of evidence, and produced an evidence report. An expert Voting Panel reviewed the evidence and formulated recommendations. The panel

This article is published simultaneously in *Arthritis & Rheumatology*.
Supported by the American College of Rheumatology.
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included adult and pediatric rheumatology providers, infectious diseases specialists, and patient representatives. Consensus required ≥70% agreement on both the direction and strength of each recommendation.

Results. This guideline includes expanded indications for some vaccines in patients with RMDs, as well as guidance on whether to hold immunosuppressive medications or delay vaccination to maximize vaccine immunogenicity and efficacy. Safe approaches to the use of live attenuated vaccines in patients taking immunosuppressive medications are also addressed. Most recommendations are conditional and had low quality of supporting evidence.

Conclusion. Application of these recommendations should consider patients' individual risk for vaccine-preventable illness and for disease flares, particularly if immunosuppressive medications are held for vaccination. Shared decision-making with patients is encouraged in clinical settings.

INTRODUCTION

Rheumatic and musculoskeletal diseases (RMDs) (1,2) and immunosuppressive medications used to treat them place patients at higher risk of vaccine-preventable infections and of more serious complications of infection. Vaccines have long been used to reduce illness from common viral and bacterial pathogens, and standardized vaccine schedules for children and adults have been widely adopted for use in both healthy people and those with chronic medical conditions (3,4). However, the immunogenicity and safety of vaccines may differ in patients with RMDs compared to the general population, and patients with RMDs may benefit from modified vaccine indications and/or adjustments to vaccination or medication schedules. Issues related to vaccination and medication management at the time of vaccination apply across diseases, and thus, this guideline is meant to help in the management of vaccines for all children and adults with RMDs in the US. The target audience is limited to rheumatology providers in the US because the epidemiology of vaccine-preventable infections and the availability of specific vaccines vary across the globe. However, providers in other countries may also find the guideline useful. A list of specific medications, vaccinations, and RMDs addressed in this guideline is found in Table 1, and a glossary of terms commonly used in this guideline can be found in Table 2.

Avacopan and bimekizumab, the pneumococcal vaccines PCV15 and PCV20, and the smallpox/monkeypox vaccine were not included in the formal evidence review because they were not approved at the time of the project plan. Antipyretic medications such as nonsteroidal antiinflammatory drugs and acetaminophen were also not included. Although a few randomized controlled trials (RCTs) have demonstrated blunted antibody responses with antipyretics, this was seen after primary vaccination only, and not after booster (5) or influenza vaccination (6). Observational studies also suggest that they have minimal-to-no impact on antibody responses to vaccination (5,7). Vaccinations against COVID-19 are not included in this guideline because, given the fast-changing nature of the pandemic and the COVID-19–related literature, there was concern that recommendations would be obsolete well before guideline publication. COVID-19 vaccinations will be incorporated into a future guideline update once the pertinent literature has stabilized. We refer readers to the American College of Rheumatology (ACR) COVID-19 vaccine guidance (8) and to the Centers for Disease Control and Prevention (CDC) website (9) for information on COVID-19 vaccines for patients with compromised immunity. Finally, we refer readers to the Advisory Committee on Immunization Practices (ACIP) (10) and the American Academy of Pediatrics (AAP) (11) vaccination guidelines for any other topics not addressed herein. This study did not involve human subjects, and therefore, approval from Human Studies Committees was not required.

The 2022 ACR guideline for vaccination in adults and children with RMDs highlights the following: 1) pneumococcal vaccination should be administered to all RMD patients taking immunosuppressive medication; 2) recombinant zoster vaccination is recommended for RMD patients >18 years of age taking immunosuppressive medication; 3) methotrexate should be held

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr.25045&file=acr25045-sup-0001-Disclosureform.pdf.

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Submitted for publication August 8, 2022; accepted in revised form October 13, 2022.

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Table 1. Guideline scope*

Medications		Vaccines†		Rheumatic and musculoskeletal disorders
Immunosuppressive	Nonimmunosuppressive	Non–live attenuated	Live attenuated	
Glucocorticoids Prednisone Methylprednisolone Dexamethasone Hydrocortisone csDMARDs Methotrexate Leflunomide Azathioprine Mycophenolate mofetil/ mycophenolic acid Calcineurin inhibitors (cyclosporine, tacrolimus, voclosporin) Cyclophosphamide bDMARDs TNF inhibitors (etanercept, adalimumab, certolizumab, golimumab, infliximab) IL-6R inhibitors (tocilizumab, sarilumab) IL-17 inhibitors (secukinumab, ixekizumab) IL-12/23 inhibitors (ustekinumab) IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab) IL-1 inhibitors (anakinra, canakinumab, rilonacept) T cell costimulation inhibitor (CTLA4-Ig/ abatacept) B cell–depleting agents (rituximab, ocrelizumab, obinutuzumab) BLyS/BAFF inhibitors (belimumab, tabalumab) Interferon-α receptor inhibitor (anifrolumab) tsDMARDs JAK inhibitors (tofacitinib, baricitinib, upadacitinib, filgotinib, ruxolitinib)	Hydroxychloroquine Sulfasalazine Colchicine Apremilast Denosumab IVIG	Seasonal influenza Standard dose, high dose, adjuvanted Pneumococcal PPSV23, PCV13‡ Other Hemophilus influenza b Hepatitis A Hepatitis B Human papillomavirus Inactivated polio Meningococcus B Meningococcus ACWY Tetanus toxoid/Td/Tdap Typhoid (injectable) Zoster subunit	Influenza (intranasal) MMR Rotavirus Typhoid (oral) Varicella Yellow fever Zoster	Inflammatory arthropathies Rheumatoid arthritis Psoriatic arthritis Ankylosing spondylitis Spondyloarthritis Enthesitis-related arthritis IBD-associated arthritis Juvenile idiopathic arthritis Connective tissue diseases Systemic lupus erythematosus Sjögren's syndrome Systemic sclerosis Idiopathic inflammatory myopathies Mixed connective tissue disease Undifferentiated connective tissue disease Antiphospholipid antibody syndrome Vasculitides Granulomatosis with polyangiitis Microscopic polyangiitis Eosinophilic granulomatosis with polyangiitis Giant cell arteritis Polyarteritis nodosa Takayasu arteritis Cryoglobulinemic vasculitis Relapsing polychondritis Behçet's disease Kawasaki disease IgA vasculitis (Henoch-Schönlein) Primary CNS vasculitis Goodpasture's syndrome (anti-GBM) Cogan's syndrome Cutaneous small vessel vasculitis Rheumatoid vasculitis Urticarial vasculitis Other inflammatory disorders Sarcoidosis Adult-onset Still's disease Polymyalgia rheumatica Gout Pseudogout IgG4-related disease Autoinflammatory disorders

* MMR = measles, mumps, and rubella (vaccine); PPSV23 = pneumococcal polysaccharide vaccine; PCV13 = pneumococcal conjugate vaccine; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; IVIG = intravenous immunoglobulin; IBD = inflammatory bowel disease; bDMARDs = biologic DMARDs; TNF = tumor necrosis factor; IL-6R = interleukin-6 receptor; BLyS = B lymphocyte stimulator; tsDMARDs = targeted synthetic DMARDs; CNS = central nervous system; anti-GBM = anti–glomerular basement membrane (disease).
† COVID-19 vaccines were not included in this guideline because of the fast-changing face of the pandemic and related literature.
‡ The recently approved pneumococcal vaccines, PCV15 and PCV20, were not included in the evidence review but are discussed in the text with reference to current Centers for Disease Control and Prevention guidelines.

for 2 weeks after influenza vaccination if disease activity allows; 4) seasonal influenza vaccination should be administered to RMD patients even if their disease is active, they are taking high-dose glucocorticoids, and/or they are taking rituximab; 5) in RMD patients taking rituximab, vaccines other than for influenza should be administered at least 6 months after the last rituximab

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Table 2. Glossary of terms

Term	Definition
Adjuvant	An ingredient used in some vaccines that helps create a stronger immune response in patients receiving the vaccine
Immunogenicity	The ability of a vaccine to elicit an immune response
Reactogenicity	Typical symptoms (e.g., fever, sore arm, muscle aches) that occur shortly (days) after vaccine administration either at the site of vaccination or systemically
Seroconversion	Development of antibodies to a pathogen, elicited by a vaccine (or infection), in the blood of an individual who previously did not have detectable antibodies
Seroprotection	An antibody level capable of protecting against infection or disease
Titer	Numerical value indicating the level of antibody against a particular pathogen

dose; and 6) infants exposed to tumor necrosis factor inhibitors (TNFi) in utero should receive rotavirus vaccination in the first 6 months of life.

METHODS

This guideline follows ACR policy guiding management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) and the ACR guideline development process, which includes Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (12,13), and adheres to the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria (14). Supplementary Appendix 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25045, includes a detailed description of the methods. Briefly, the guideline team drafted clinical population, intervention, comparator, outcomes (PICO) questions (see Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25045). The literature review team performed a systematic literature review for the PICO questions, graded the quality of evidence (high, moderate, low, very low), and produced the evidence report (see Supplementary Appendix 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25045). An expert Voting Panel reviewed the evidence report and then formulated and voted on recommendations. Additionally, a virtual Patient Panel reviewed the evidence and provided patient perspectives and preferences for consideration by the Voting Panel. The Patient Panel consisted of 9 patients with a variety of adult and pediatric RMDs and was moderated by a member of the core team (EC).

Voting Panel consensus required ≥70% agreement on both the direction (for or against) and strength (strong or conditional) of each recommendation, as per ACR practice. According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when costs are expected to impact the decision. Thus, for conditional recommendations, incorporation of patient preferences is particularly essential, acknowledging that patient preferences are an important part of all clinical decision-making. Rosters of the Core Leadership Team, Literature Review Team, Voting Panel, and Patient Panel are included in Supplementary Appendix 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25045.

The following guiding principles were used in this guideline: 1) indicated vaccinations should be given to patients whenever possible; 2) this guideline is complementary to recommendations from the ACIP (10) and the AAP (15); 3) the decision to hold a medication before or after vaccination should consider the patient's disease, disease activity, and risk for vaccine-preventable infection; and 4) shared decision-making with patients is a key component of any vaccination strategy.

RESULTS/RECOMMENDATIONS

Expanded indications for specific vaccines in patients with RMDs receiving immunosuppression

Influenza vaccination

For patients with RMD age ≥65 years and patients with RMD age >18 years and <65 years who are taking immunosuppressive medication, giving high-dose or adjuvanted influenza vaccination is conditionally recommended over giving regular-dose influenza vaccination.

Any influenza vaccine is preferred over no influenza vaccine, and vaccination "today" is preferred over delay. Therefore, if high-dose or adjuvanted influenza vaccine is not available in the clinic during a patient visit when influenza vaccination is indicated, then standard-dose influenza vaccine should be administered. This caveat also applies in instances when insurance restrictions may preclude administration of high-dose or adjuvanted influenza vaccination to patients <65 years of age.

High-dose influenza vaccine is a quadrivalent vaccine containing 4 times the antigen as the standard-dose vaccine. Two RCTs in rheumatoid arthritis (RA) patients showed higher seroconversion rates in younger patients receiving high-dose vaccination compared to standard-dose vaccination with no safety signal (16,17). The adjuvanted influenza vaccine is a standard-dose quadrivalent vaccine containing the MF59 adjuvant, which elicits a strong antigenic response without the need for a higher antigen dose. No studies of the adjuvanted influenza vaccination in RMD patients age <65 years were identified in the literature search, but there

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have been no safety issues seen with adjuvants in general, although they may be associated with greater reactogenicity (18).

Pneumococcal vaccination

For patients with RMD age <65 years who are taking immunosuppressive medication, pneumococcal vaccination is strongly recommended.

Patients with RMDs taking immunosuppressive medication may be at increased risk of pneumococcal infection (19,20). Multiple observational studies have evaluated the prime boost method of pneumococcal vaccination, with a pneumococcal conjugate vaccine (PCV13 or PCV15), followed 2 months later by a dose of the pneumococcal polysaccharide vaccine (PPSV23). A single-dose PCV20 vaccine is now approved in the US (21) and is likely to supplant this 2-dose strategy in the not-too-distant future, at least in adults. PCV15 and PCV20 polysaccharide conjugates are not currently approved for use in children in the US; but this too may soon change. The CDC currently recommends PCV15 followed by PPSV23 one year later, or PCV20, for adults <65 years taking immunosuppressive medications who were not previously vaccinated against pneumococcus, however, we recommend reference to CDC guidelines when choosing a specific pneumococcal vaccination strategy because this area is rapidly changing (21).

There are few studies evaluating the impact of disease-modifying antirheumatic drugs (DMARDs) on conjugate pneumococcal vaccines. The ACIP recommends administering pneumococcal vaccination to individuals age >18 years with certain chronic medical conditions and those taking immunosuppressive medication (10,22). The CDC and AAP recommend the primary PCV13 series to all children <2 years of age and PPSV23 vaccination to children age ≥2 years with underlying medical conditions (15).

Recombinant varicella-zoster virus (VZV) vaccination

For patients with RMD age >18 years who are taking immunosuppressive medication, administering the recombinant VZV vaccine is strongly recommended.

Patients with RMDs such as systemic lupus erythematosus (SLE) and RA are at higher risk of herpes zoster than older adults recommended for vaccination (23). Although the literature search identified no publications that specifically addressed recombinant VZV vaccination in patients with RMDs who are <50 years of age, this vaccine has been shown to be safe and effective in immunosuppressed patients undergoing renal transplantation (24) and autologous stem cell transplantation (25) and in patients with hematologic malignancies, many of whom are <50 years of age (26,27). The ACIP recommends recombinant VZV vaccination for individuals >18 years and <50 years of age who are immunocompromised and for the general public age ≥50 years (10). One retrospective study demonstrated mild disease flares in some patients around the time of vaccination (28), and reactogenicity is common with this vaccine (26).

Human papillomavirus (HPV) vaccination

For patients with RMD age >26 years and <45 years who are taking immunosuppressive medication and not previously vaccinated, vaccination against HPV is conditionally recommended.

Patients taking immunosuppressive medication may be at increased risk of cervical dysplasia and cervical cancer (29–33). Two studies of young patients with SLE (mean age 38 years and 26 years in the 2 studies, respectively) demonstrated that vaccination against HPV was immunogenic and well tolerated (34,35). The ACIP recommends HPV vaccination for individuals ages 11–26 years. For those ages 26–45 years who have not been previously vaccinated, ACIP recommends HPV vaccination based on shared decision-making (10). The benefits of vaccination after age 45 years diminish due to the greater likelihood of previous exposure to HPV.

Whether to hold immunosuppressive medication at the time of non–live attenuated vaccination to maximize vaccine immunogenicity, although holding medications could be associated with disease flare (Table 3).

Methotrexate

For patients with RMD, *holding* methotrexate for 2 weeks after influenza vaccination is conditionally recommended, assuming disease activity allows.

For patients with RMD, continuing immunosuppressive medications other than methotrexate around the time of influenza vaccination is conditionally recommended.

For patients with RMD, continuing immunosuppressive medications around the time of other (non-influenza) non–live attenuated vaccinations is conditionally recommended.

Many observational studies (36,37) suggest that methotrexate significantly blunts but does not completely abrogate the immunogenicity of influenza vaccination. Two RCTs demonstrated a beneficial impact of holding methotrexate around the time of influenza vaccination on vaccine immunogenicity (38,39). Assessment of flare risk and shared decision-making with the patient is recommended when deciding whether methotrexate should be held. Non-rheumatology providers (e.g., general pediatricians and internists) are encouraged to give influenza vaccination even if they are unsure as to whether to hold methotrexate, and then to consult with the patient's rheumatologist, rather than miss a vaccination opportunity. The literature review did not identify any studies that addressed holding medications in the context of vaccines other than for influenza. However, 2 studies published after completion of the literature review suggested that

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Table 3. Medication management at the time of non–live attenuated vaccine administration

	Influenza vaccination	Other non–live attenuated vaccinations
Methotrexate	Hold methotrexate for 2 weeks *after* vaccination*	Continue methotrexate
Rituximab	Continue rituximab†	Time vaccination for when the next rituximab dose is due, and then hold rituximab for at least 2 weeks after vaccination
Immunosuppressive medications other than methotrexate and rituximab	Continue immunosuppressive medication	Continue immunosuppressive medication

□ = Conditional recommendation.
* Hold only if disease activity allows. Non-rheumatology providers, e.g., general pediatricians and internists, are encouraged to give the influenza vaccination and then consult with the patient's rheumatology provider about holding methotrexate to avoid a missed vaccination opportunity.
† Give influenza vaccination on schedule. Delay any subsequent rituximab dosing for at least 2 weeks after influenza vaccination if disease activity allows.

holding methotrexate at the time of COVID-19 vaccination is associated with greater vaccine immunogenicity (40,41).

The literature review identified no studies that directly addressed the impact of holding medications other than methotrexate at the time of influenza vaccination. Two RCTs performed in patients initiating TNFi versus placebo demonstrated similar responses to influenza vaccination in the 2 arms (42,43). Data on other biologic DMARDs and their relationship to influenza vaccine responses are much more limited (44–47).

Rituximab

For patients with RMD receiving rituximab, administering influenza vaccination on schedule is conditionally recommended rather than deferring vaccination until the next rituximab administration is due.

For patients with RMD receiving rituximab, *deferring* non–live attenuated vaccinations, other than influenza vaccination, until the next rituximab administration is due, and *delaying* rituximab for 2 weeks after vaccination, is conditionally recommended.

Influenza vaccine responses are greater when the vaccine is administered later rather than earlier after rituximab (48–50). Rituximab has also been shown to blunt responses to pneumococcal polysaccharide PPSV23 vaccination (51,52). Because of the seasonal nature of influenza, influenza vaccination is conditionally recommended to be given on schedule to patients receiving rituximab. For other non–live attenuated vaccinations, deferring vaccination until the next rituximab dose will improve vaccine immunogenicity. However, patients could also be vaccinated in the interest of acquiring some immunity and then revaccinated later (influenza vaccination could also be repeated using this same rationale). Whenever possible, vaccinations should be administered prior to rituximab initiation. Rituximab should be delayed for at least 2 weeks after any vaccination to allow time for the patient to develop an immune response, assuming that disease activity allows.

Whether to administer non–live attenuated vaccinations to patients receiving glucocorticoids or with active disease (Table 4).

Glucocorticoids

Whether to administer non–live attenuated vaccinations to patients taking glucocorticoids or defer vaccination to a later time point to maximize vaccine immunogenicity.

For patients with RMD who are taking the equivalent of prednisone ≤10 mg daily, administering any non–live vaccinations is strongly recommended.

For patients with RMD who are taking the equivalent of prednisone >10 mg daily but <20 mg daily, administering any non–live attenuated vaccinations is conditionally recommended.

For patients with RMD taking the equivalent of prednisone ≥20 mg daily, administering influenza vaccination is conditionally recommended.

For patients with RMD who are taking the equivalent of prednisone ≥20 mg daily, *deferring* non–live attenuated vaccinations, other than influenza vaccination, until glucocorticoids are tapered to the equivalent of prednisone <20 mg daily is conditionally recommended.

Most studies that have compared prednisone <10 mg daily to prednisone ≥10 mg daily found that the higher dosages did reduce influenza vaccine immunogenicity (53–55). Several studies that defined high-dose glucocorticoids as prednisone ≥20 mg daily observed that they blunted patients' vaccine response (56–58). Two studies that examined glucocorticoid dosage as a continuous variable identified a dose–response relationship while suggesting against a specific dose threshold (57,58). Evidence for the impact of glucocorticoids on responses to other vaccines is less consistent (59–61). For some vaccines, humoral responses can be measured and revaccination considered in those with an inadequate response.

Given the importance of timely influenza vaccination, a conditional recommendation was made to administer influenza vaccination to patients receiving the equivalent of prednisone ≥20 mg daily. For vaccines other than for influenza, a conditional

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Table 4. Whether to give or defer non–live attenuated vaccinations in patients taking glucocorticoids regardless of disease activity

	Influenza vaccination	Other non–live attenuated vaccinations
Prednisone ≤10 mg daily*	Give	Give
Prednisone >10 mg and <20 mg*	Give	Give
Prednisone ≥20 mg daily*	Give	Defer†

■ = Strong recommendation.
□ = Conditional recommendation.
* Or the equivalent dose of any other glucocorticoid formulation, or the equivalent pediatric dose.
† Defer vaccination until glucocorticoids are tapered to the equivalent of prednisone <20 mg daily.

recommendation was made to delay vaccination until the dose is lower to maximize vaccine efficacy. It is understood, however, that some patients may not be able to delay, e.g., children who require vaccination for school entry.

Disease activity

Whether to defer vaccination in patients with high disease activity to maximize vaccine immunogenicity and/or avoid worsening disease activity.

For patients with RMD, giving non–live attenuated vaccinations is conditionally recommended regardless of patients' disease activity.

Patients with RMD often express concern about whether vaccination can induce a disease flare, but the vast majority of studies failed to show any increased rate of flare after influenza vaccination. The results were similar for other vaccinations, although the quality of the evidence was low. Strong concerns, however, were expressed among the Patient Panel about the potential for vaccines to cause a disease flare, and shared decision-making is particularly important in this setting. Most studies suggest that increased disease activity does not impact vaccine immunogenicity (53,62), although one study did show lower seroconversion rates in pediatric lupus patients with a Systemic Lupus Erythematosus Disease Activity Index score of >8 who were vaccinated against influenza (57).

Managing immunosuppressive therapy at the time of live attenuated vaccination to avoid vaccine-associated illness (Table 5).

For patients with RMD who are taking immunosuppressive medication, *deferring* live attenuated vaccines is conditionally recommended.

For patients with RMD, *holding* immunosuppressive medication for an appropriate period before and 4 weeks after live attenuated virus vaccination is conditionally recommended.

For some live attenuated virus vaccines, such as for oral polio, oral typhoid, and influenza, there are inactivated alternatives that can be safely given to RMD patients taking immunosuppressive medication.

Conventional DMARDs. Two observational studies in patients with RMDs who were only taking conventional DMARDs and/or prednisone <20 mg daily at the time they received the yellow fever vaccine observed no cases of infection (63,64). Similarly, in a retrospective cohort study of patients with juvenile idiopathic arthritis (JIA) taking methotrexate and vaccinated against measles, mumps, and rubella (MMR), none developed vaccine-associated disease (65). Some pediatric rheumatologists do recommend giving live attenuated virus vaccine boosters (66) to children receiving low-dose immunosuppression when the child is likely to be taking the medication long term and when the risk of flare when not receiving immunosuppression is high, especially in areas with low community vaccination rates and/or during outbreaks (67). The AAP Red Book (15) and the Infectious Diseases Society of America (68) define low-level immunosuppression as methotrexate ≤0.4 mg/kg/week, azathioprine ≤3 mg/kg/day, prednisone <20 mg/day (or <2 mg/kg/day for patients weighing <10 kg), or alternate-day glucocorticoid therapy (68).

Biologic DMARDs. In a large RCT of RMD patients taking TNFi who were given the live attenuated VZV vaccine, there were no confirmed cases of varicella infection in either the vaccine or placebo group during 1 year of follow-up (69). Similarly, in an observational study of patients with Kawasaki disease who received vaccines against rotavirus and/or MMR plus varicella within 90 days prior to a single dose of infliximab, none experienced any serious infections (70). Finally, in a study of RA patients given a yellow fever booster 1 month after their last dose of infliximab, none developed symptoms of yellow fever (71).

In contrast, in a very small retrospective study based on an email survey to pediatric and adult rheumatologists and immunologists that reported on 17 children with autoinflammatory disorders or systemic JIA taking interleukin-1 or interleukin-6 receptor inhibitors and who were given a variety of live attenuated vaccinations, 3 of 17 patients developed vaccine-associated infection, and 7 of 17 patients experienced disease flares (72).

JAK inhibitors. Cutaneous vaccine-strain varicella infection developed in 1 of 55 RA patients given a single dose of the live attenuated VZV vaccine 2–3 weeks prior to tofacitinib initiation in the context of an RCT. Later testing demonstrated that the study participant lacked prevaccination immunity to VZV (73). Complete lack of immunity to varicella is rare in adults in the US, where the prevalence of varicella seropositivity is 98% in adults (74).

Intravenous immunoglobulin (IVIG). Antiviral antibodies contained in IVIG can interfere with replication of live attenuated vaccines and reduce their efficacy (75). The CDC recommends a delay of 8–11 months (depending on IVIG dose) between receipt of high-dose IVIG and live attenuated virus vaccination (76). However, there will be situations, such as during a measles outbreak,

Table 5. Immunosuppressive medication management at the time of live attenuated virus vaccine administration*

	Hold before live attenuated virus vaccine administration	Hold after live attenuated virus vaccine administration
Glucocorticoids†	4 weeks	4 weeks
Methotrexate, azathioprine‡	4 weeks	4 weeks
Leflunomide, mycophenolate mofetil, calcineurin inhibitors, oral cyclophosphamide	4 weeks	4 weeks
JAK inhibitors	1 week	4 weeks
TNF, IL-17, IL-12/23, IL-23, BAFF/BLyS inhibitors	1 dosing interval§	4 weeks
IL-6 pathway inhibitors	1 dosing interval¶	4 weeks
IL-1 inhibitors		
Anakinra	1 dosing interval¶	4 weeks
Rilonacept	1 dosing interval¶	4 weeks
Canakinumab	1 dosing interval¶	4 weeks
Abatacept	1 dosing interval§	4 weeks
Anifrolumab	1 dosing interval§	4 weeks
Cyclophosphamide, intravenous	1 dosing interval§	4 weeks
Rituximab	6 months	4 weeks
IVIG#		
300–400 mg/kg	8 months	4 weeks
1 gm/kg	10 months	4 weeks
2 gm/kg	11 months	4 weeks

* TNF = tumor necrosis factor; IL = interleukin; BLyS = B lymphocyte stimulator; IVIG = intravenous immunoglobulin.
† For patients taking the equivalent of prednisone <20 mg/day or <2 mg/kg/day for patients weighing <10 kg or alternate-day glucocorticoid therapy (i.e., "low-level immunosuppression" [15,68]), these low doses can be continued if vaccination is critical and the risk of a disease flare or adrenal insufficiency when the patient is not taking glucocorticoids is high.
‡ For patients taking methotrexate ≤0.4 mg/kg/week or azathioprine ≤3 mg/kg/day ("low-level immunosuppression" [15,68]), hold times can be shortened if vaccination is critical and the risk of a disease flare when the patient is not taking immunosuppression is high.
§ For medications with >1 dosing interval approved by the Food and Drug Administration, the longest interval should be chosen (e.g., hold subcutaneous adalimumab for 2 weeks, although it can be dosed every 1 or every 2 weeks).
¶ In children with autoinflammatory disorders or systemic juvenile idiopathic arthritis in whom the risk of disease flare if biologic disease-modifying antirheumatic drugs are held is very high, shorter hold times can be considered if live attenuated vaccination is critical.
# The recommendation to hold IVIG prior to vaccination is designed to enhance vaccine efficacy, not safety. In some situations, such as during a measles outbreak, earlier vaccination would be preferred over delay.

when earlier vaccination is preferred over delay because some immunity will be preferred over none in that setting.

Specific recommendations for holding medications if live attenuated vaccines are given. Although the evidence around the safety of conventional DMARDs and TNFi at the time of live attenuated virus vaccination is reassuring, the total number of RMD patients who have been studied is small, and the Voting Panel conditionally recommended against administering live attenuated virus vaccines to patients receiving those agents as well as other forms of immunosuppression. For patients who do need to receive live attenuated vaccines, specific recommendations for holding immunosuppressive medications around the time of vaccination can be found in Table 5.

For slow-acting conventional DMARDs, a prevaccination hold time of 4 weeks was chosen to reflect their prolonged duration of action. However, direct evidence for the optimal hold time is lacking. For most biologic DMARDs, a hold time of 1 dosing interval before live attenuated vaccine administration is recommended.

The number of RMD patients who are taking immunosuppressive medications at the time that they need live attenuated virus vaccines is small. However, very young children, especially those with autoinflammatory disorders, may require biologic DMARDs before their primary vaccination series is complete. In these children, the risk associated with a disease flare may be considerably higher than the risk associated with the vaccine preventable illness (72). Children with autoinflammatory disorders also often require lifelong anticytokine therapy, and there may never be an opportunity to catch up on missed vaccinations later. For these children, shorter medication hold times can be considered if live attenuated virus vaccination is critical and cannot be delayed. Shared decision-making with the child's parents/guardians is important in this setting, and they should be alerted to the signs and symptoms of attenuated vaccine-associated infection.

The recommendation to hold immunosuppressive medications for 4 weeks after live attenuated vaccination is conservative. Typically, the duration of viremia (live virus circulating in the blood) after live attenuated vaccination is 2 weeks, although it can be longer in some patients (77). Viremia is more prolonged after primary vaccination than after booster vaccinations (77). Medication hold times after vaccination can be shortened if vaccination is critical and the risk of a disease flare when the patient is not receiving immunosuppression is high.

Close contacts of immunosuppressed patients should receive all age-appropriate vaccination (with the exception of smallpox) to avoid the vaccine-preventable diseases, as recommended by the ACIP (78). The ACIP also notes that no specific precautions are needed except if a household contact develops a rash after varicella vaccination, in which case direct contact should be avoided until the rash resolves (78). They also reinforce the recommendation to household members to wash their hands after diaper changing when an infant has received a rotavirus vaccine (78).

When to administer rotavirus vaccine to infants with second- and/or third-trimester antenatal exposure to biologic DMARDs in utero (Table 6).

For neonates/infants with second- and/or third-trimester antenatal exposure to TNFi, giving live attenuated rotavirus vaccine within the first 6 months of life is conditionally recommended.

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For neonates/infants with second- and/or third-trimester antenatal exposure to rituximab, *delaying* live attenuated rotavirus vaccine until >6 months of age is conditionally recommended.

Vaccination against rotavirus typically occurs at 2 and 4 months, or at 2, 4, and 6 months. Rotavirus is rare in the US because of widespread immunization, and for this reason, the AAP recommends delaying rotavirus vaccination for 12 months after any in utero exposure to biologic DMARDs (except for certolizumab, which does not cross the placenta) (15). Three observational studies encompassing 58 children exposed to biologic DMARDs (most taking TNFi) who received live rotavirus vaccines reported no clear adverse events (79–81). Only minimal amounts of infliximab have been detected in the breast milk of treated patients (82).

The literature review identified no data on the effect of in utero rituximab exposure on later vaccine responses. Rituximab is a chimeric IgG1 molecule that can cross the placenta, and it has been associated with low or absent B lymphocyte levels in newborns who were exposed during the second or third (but not the first) trimester (83). Most reports demonstrate B cell recovery in these infants within 6 months after birth (83). Extrapolating from vaccine responses in adults treated with rituximab (48–50), infants exposed to rituximab are unlikely to respond to vaccination until 6 months postexposure. Although delayed rotavirus vaccine administration has been associated with an increased risk of intussusception, this complication remains quite rare (84).

After giving birth, most RMD patients turn to their general pediatrician rather than to their adult rheumatology provider for infant vaccination recommendations, and pediatricians may not be aware of the impact of in utero medication exposure on vaccine safety and immunogenicity. Therefore, recommendations regarding infant rotavirus vaccination after in utero exposure to either TNFi or rituximab should be discussed with the pregnant RMD patient prior to delivery. Specifically, the pregnant patient should be educated as to the fact that medications that cross the placenta may affect vaccination schedules for their infants. A copy of the current vaccine guideline summary (https://www.rheumatology.org/Portals/0/Files/Vaccinations-Guidance-Summary.pdf) may serve as a useful resource for the pregnant RMD patient to share with their pediatrician in advance of delivery.

Table 6. When to administer live attenuated rotavirus vaccination to infants exposed to immunosuppressive medications in utero*

Antenatal drug exposure in second or third trimester	Within the first 6 months of life	After 6 months of life
TNFi	Give rotavirus vaccine	–
Rituximab	Do not give rotavirus vaccine	Give rotavirus vaccine

□ = Conditional recommendation.
* TNFi = tumor necrosis factor inhibitor.

Whether to give multiple vaccinations to patients with RMD on the same day.

For patients with RMD, giving multiple vaccinations on the same day rather than giving each individual vaccination on a different day is conditionally recommended.

Administering >1 vaccination on a single day is a routine practice in both pediatric and adult medicine that is supported by the CDC in order to avoid a missed vaccination opportunity (85). Patient representatives on the Voting Panel felt that shared decision-making was important in this instance due to their concerns about the potential for reactogenicity or disease flare.

A summary of the guideline recommendations, associated PICO questions, and level of evidence can be found in Table 7.

DISCUSSION

This is the first guideline to address vaccination strategies across the entire adult and pediatric RMD spectrum. An underlying principle in this guideline is that patients should be vaccinated, and that missed vaccination opportunities should be avoided or minimized. This is particularly true regarding influenza vaccination, which is administered seasonally and is recommended for RMD patients even if their disease activity is high, they are taking high-dose glucocorticoids, and/or are taking rituximab. The Voting Panel generally favored simple recommendations to encourage vaccination and foster guideline adherence. There are few studies assessing the immunogenicity and safety of specific vaccines in relation to specific immunosuppressive medications, and there are virtually no studies assessing the impact of holding medications around the time of vaccination, particularly for vaccines other than for influenza. Therefore, many of the recommendations are conditional and apply across diseases, vaccines, medications, and age groups. Because of the low quality of the evidence, shared decision-making between clinicians and patients/parents/guardians is particularly important for the vaccination strategies presented here. These recommendations do not supersede clinical judgement.

Most recommendations in this guideline are aimed at maximizing vaccine immunogenicity because the literature revealed few vaccine safety signals, at least regarding non-live vaccinations. Many vaccines are required for school entry to protect not only the health of the individual but also that of the broader community. Public health requirements may supersede some recommendations made here. Insurance barriers could inhibit implementation of these recommendations, such as to administer high dose or adjuvanted influenza vaccine or recombinant VZV to RMD patients <65 years of age taking immunosuppressive medications. In such instances, this guideline could be used as a resource to aid in prior authorization.

Not included in this guideline are recommendations for COVID-19 vaccination in patients with RMD. Readers can refer to the CDC for the most up-to-date recommendations for COVID-19 vaccination, including for patients taking immunosuppressive

Table 7. Summary of recommendations*

Recommendations	Level of evidence†	PICO	Evidence table page numbers
Expanded indications for specific vaccines in patients with RMDs receiving immunosuppression			
Influenza vaccination			
For patients with RMD age ≥65 years and patients with RMD age >18 and <65 years who are taking immunosuppressive medication, giving high-dose or adjuvanted influenza vaccination is **conditionally** recommended over giving regular-dose influenza vaccination.	PICO 9. Very low (indirect evidence only)‡	PICO 9. In patients with RMD age ≥65 years, is high-dose influenza vaccine more effective than seasonal regular-dose influenza vaccine?	728
	PICO 10. Very low (indirect evidence only)‡	PICO 10. In patients with RMD age ≥65 years, is adjuvanted influenza vaccine more effective than seasonal regular-dose influenza vaccine?	728
	PICO 11. Moderate	PICO 11. In patients with RMD <65 years of age, is high- dose vaccine more effective than seasonal regular-dose influenza vaccine?	728–737
	PICO 12. Very low (indirect evidence only)‡	PICO 12. In patients with RMD <65 years of age, is adjuvanted influenza vaccine more effective than seasonal regular-dose influenza vaccine?	737
Pneumococcal vaccination			
For patients with RMD age <65 years who are taking immunosuppressive medication, pneumococcal vaccination is **strongly** recommended.	PICO 20. Low	PICO 20. Should patients with RMD receive vaccination against pneumococcus at age <65 years?	933–952
Recombinant VZV vaccination			
For patients with RMD age >18 years who are taking immunosuppressive medication, administering the recombinant VZV vaccine is **strongly** recommended.	PICO 21. Very low (indirect evidence only)‡	PICO 21. Should patients with RMD receive VZV vaccination at age <50 years?	952
HPV vaccination			
For patients with RMD age >26 and <45 years who are taking immunosuppressive medication and are not previously vaccinated, vaccination against HPV is **conditionally** recommended.	PICO 19. Very low	PICO 19. Should patients with RMD be vaccinated against HPV at age >26 years?	931–933
Whether to hold immunosuppressive medication at the time of non–live attenuated vaccination to maximize vaccine immunogenicity, although holding medications could be associated with disease flare			
For patients with RMD, *holding* methotrexate for 2 weeks after influenza vaccination is **conditionally** recommended, assuming disease activity allows.	PICO 3. Very low for most comparisons, moderate for a few	PICO 3. In patients with [RMD disease X], what is the effect of [drug Y/drug class] on immunization responses to [vaccine Z, vaccine type] in comparison with [general population, or drug Y]?	7–550
	PICO 15. TNFi: low; tocilizumab: very low; secukinumab: very low; tofacitinib: moderate; glucocorticoids: very low; abatacept: very low	PICO 15. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients taking drug Y as compared to those not taking drug Y at the time of vaccination?	754–898
	PICO 16. MTX: moderate; tofacitinib: low; other medications: indirect evidence only	PICO 16. Should patients with RMD taking drug Y hold their drug Y for a period of time prior to or after receiving (not live attenuated) vaccines?	898–927

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Table 7. (*Cont'd*)

Recommendations	Level of evidence†	PICO	Evidence table page numbers
For patients with RMD, continuing immunosuppressive medications other than methotrexate around the time of influenza vaccination is **conditionally** recommended.	PICO 3. Very low for most comparisons, moderate for a few	PICO 3. In patients with [RMD disease X], what is the effect of [drug Y/drug class] on immunization responses to [vaccine Z, vaccine type] in comparison with [general population, or drug Y]?	7–550
	PICO 15. TNFi: low; tocilizumab: very low; secukinumab: very low; tofacitinib: moderate; glucocorticoids: very low; abatacept: very low	PICO 15. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients taking drug Y as compared to those not taking drug Y at the time of vaccination?	754–898
	PICO 16. MTX: moderate; tofacitinib: low; other medications: indirect evidence only	PICO 16. Should patients with RMD taking drug Y hold their drug Y for a period of time prior to or after receiving (not live attenuated) vaccines?	898–927
For patients with RMD, continuing immunosuppressive medications around the time of other (non-influenza) non–live attenuated vaccinations is **conditionally** recommended.	PICO 3. Very low for most comparisons, moderate for a few	PICO 3. In patients with [RMD disease X], what is the effect of [drug Y/drug class] on immunization responses to [vaccine Z, vaccine type] in comparison with [general population, or drug Y]?	7–550
	PICO 16. MTX: moderate; tofacitinib: low; other medications: indirect evidence only	PICO 16. Should patients with RMD taking drug Y hold their drug Y for a period of time prior to or after receiving (not live attenuated) vaccines?	898–927
Timing vaccinations in patients receiving rituximab to maximize vaccine efficacy			
For patients with RMD receiving rituximab, administering influenza vaccination on schedule is **conditionally** recommended rather than deferring vaccination until the next rituximab administration is due.	PICO 17. Low	PICO 17. Should patients with RMD who are taking rituximab time non–live attenuated vaccine administration relative to the next dose of medication?	927–930
For patients with RMD receiving rituximab, *deferring* non–live attenuated vaccinations, other than influenza vaccination, until the next rituximab administration is due, and *delaying* rituximab for 2 weeks after vaccination, is **conditionally** recommended.			
Whether to administer non–live attenuated vaccinations to patients receiving glucocorticoids or defer vaccination to a later time point to maximize vaccine immunogenicity			
For patients with RMD who are taking the equivalent of prednisone ≤10 mg daily, administering any non–live attenuated vaccinations is **strongly** recommended.	PICO 4. Low for pneumococcal vaccines, very low for other vaccines	PICO 4. In patients with RMD, does the immunogenicity or efficacy of vaccine Z differ in patients taking high-dose teroids as compared to those taking lower doses of steroids or those not taking steroids?	551–579
	PICO 14. Very low	PICO 14. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients taking high-dose steroids as compared to those taking lower doses of steroids or those not taking steroids?	739–754
For patients with RMD who are taking the equivalent of prednisone >10 mg daily but <20 mg daily, administering any non–live attenuated vaccinations is **conditionally** recommended.	PICO 4. Low for pneumococcal vaccines, very low for other vaccines	PICO 4. In patients with RMD, does the immunogenicity or efficacy of vaccine Z differ in patients taking high-dose steroids as compared to those taking lower doses of steroids or those not taking steroids?	551–579

(Continued)

Table 7. (*Cont'd*)

Recommendations	Level of evidence†	PICO	Evidence table page numbers
	PICO 14. Very low	PICO 14. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients taking high-dose steroids as compared to those taking lower doses of steroids or those not taking steroids?	739–754
For patients with RMD taking the equivalent of prednisone ≥20 mg daily, administering influenza vaccination is **conditionally** recommended.	PICO 14. Very low	PICO 14. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients taking high-dose steroids as compared to those taking lower doses of steroids or those not taking steroids?	739–754
For patients with RMD who are taking the equivalent of prednisone ≥20 mg daily, *deferring* non–live attenuated vaccinations, other than the influenza vaccine, until glucocorticoids are tapered to the equivalent of prednisone <20 mg daily is **conditionally** recommended.	PICO 4. Low for pneumococcal vaccines, very low for other vaccines	PICO 4. In patients with RMD, does the immunogenicity or efficacy of vaccine Z differ in patients taking high-dose steroids as compared to those taking lower doses of steroids or those not taking steroids?	551–579
Whether to defer vaccination in patients with high disease activity to maximize vaccine immunogenicity and/or avoid worsening disease activity			
For patients with RMD, giving non–live attenuated vaccinations is **conditionally** recommended regardless of patients' disease activity.	PICO 13. Very low	PICO 13. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients who have moderate to severely active underlying disease as compared to those in low disease activity or remission?	737–739
	PICO 18. Very low	PICO 18. Should moderately to severely ill patients with RMD with disease X defer vaccination (not live attenuated) until the disease is better controlled?	930–931
Managing immunosuppressive therapy at the time of live attenuated vaccination to avoid vaccine-associated illness			
For patients with RMD who are taking immunosuppressive medication, *deferring* live attenuated vaccines is **conditionally** recommended.	PICO 23. Very low	PICO 23. Should patients with RMD taking drug Y receive live attenuated vaccines?	952–960
For patients with RMD, *holding* immunosuppressive medication for an appropriate period before and 4 weeks after live attenuated virus vaccination is **conditionally** recommended.	PICO 24. Very low	PICO 24. Should patients with RMD taking drug Y hold the drug for a period of time prior to or after receiving live attenuated vaccines?	960–964
When to administer rotavirus vaccine to infants with second- and/or third-trimester antenatal exposure to biologic DMARDs in utero			
For neonates/infants with second- and/or third-trimester antenatal exposure to TNFi, giving live attenuated rotavirus vaccine within the first 6 months of life is **conditionally** recommended.	PICO 25. Very low	PICO 25. Should neonates/infants with second- and third- trimester antenatal exposure to TNFi or rituximab receive live attenuated rotavirus vaccine in their first 6 months of life?	964–966
For neonates/infants with second- and/or third-trimester antenatal exposure to rituximab, *delaying* live attenuated rotavirus vaccine until >6 months of age is **conditionally** recommended.	PICO 25. Very low	PICO 25. Should neonates/infants with second- and third- trimester antenatal exposure to TNFi or rituximab receive live attenuated rotavirus vaccine in their first 6 months of life?	964–966
Whether to give multiple vaccinations to patients with RMD on the same day			

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Table 7. (*Cont'd*)

Recommendations	Level of evidence†	PICO	Evidence table page numbers
For patients with RMD, giving multiple vaccinations on the same day rather than giving each individual vaccination on a different day is **conditionally** recommended.	PICO 22. Very low (indirect evidence only)‡	PICO 22. Should patients with RMD receive standardized regimens of vaccine combinations?	952

■ = Strong recommendation.
□ = Conditional recommendation.
* PICO = population, intervention, comparator, outcomes; RMD = rheumatic and musculoskeletal disease; VZV = varicella-zoster virus; HPV = human papillomavirus; MTX = methotrexate; TNFi = tumor necrosis factor inhibitors; DMARDs = disease-modifying antirheumatic drugs.
† The terms 'moderate', 'low', and 'very low' are based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) definitions for quality of evidence. Moderate quality means that "further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate." Low quality means that "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate." Very low quality means that "we are very uncertain about the estimate." In the systematic review for this guideline, a judgment of moderate quality required at least some evidence from randomized controlled trials, and a judgment of low quality required at least some evidence from well-designed observational studies with appropriate comparator groups.
‡ Indirect evidence indicates that there is evidence from other populations with RMD or other health conditions, or evidence that does not fully address the comparison specified in a PICO question.

medication (9). Recommendations about holding immunosuppressive medications at the time of non–live attenuated virus vaccination in this guideline (Table 3) differ from those recommended around the time of COVID-19 vaccination in the ACR COVID-19 vaccine guidance (8). This is because prior to the introduction of COVID-19 vaccines in late 2020, there was little population-level immunity to the SARS–CoV-2 virus, and maximizing vaccine efficacy was a public health imperative. In contrast, when considering routine vaccinations, the desire to avoid an RMD flare weighs more heavily in the balance. Therefore, there are very few instances where this guideline recommends holding medication at the time of non–live attenuated virus vaccination. Studies that demonstrate diminished vaccine responses in RMD patients receiving immunosuppression (other than rituximab) generally demonstrate diminished, but not completely abrogated, responses.

Finally, the literature review demonstrated that much more evidence is needed to guide practice in this area. Knowledge gaps where further research is needed are as follows: 1) standardization of trial design and outcome measures to test the efficacy and durability of response to all vaccines across all age groups; 2) safety of primary and booster live attenuated virus vaccination in children taking methotrexate and/or biologic DMARDs; 3) assessment of the immunogenicity, reactogenicity, and disease flares following standard-dose, high-dose, and adjuvanted influenza vaccination, recombinant VZV vaccination, and primary and booster COVID-19 vaccination in RMD patients taking immunosuppressive medication; and 4) RCTs to test the safety and efficacy of holding DMARDs around the time of vaccination.

ACKNOWLEDGMENTS

We thank the patients who (along with authors Ida Hakkarinen and Grayson Schultz) participated in the Patient Panel meeting: Jacob Anderson, Rachelle Crow-Hercher, Kathy Full, Sandra Nye, Mary Turner, Shilpa Venkatachalam, and Bene Williams. We thank the ACR staff, including Regina Parker, for assistance in coordinating the administrative aspects of the project, Cindy Force, for assistance with manuscript preparation, and Amy Turner, for overall supervision of the project. We thank Janet Waters for her assistance in developing the literature search strategy, as well as performing the initial literature search and update searches. We thank Susan Goodman, MD, for her help shepherding the project.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Bass had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bass, Chakravarty, Akl, Bingham, Calabrese, Cappelli, Imundo, Winthrop, Baden, Curtis, Smith, Fontanarosa, Lakin, Sadun, Tam, Turner, Reston.

Acquisition of data. Chakravarty, Calabrese, Imundo, Baden, Bridges, Schultz, Calabrese, Cunha, Fontanarosa, Gillispie-Taylor, Gkrouzman, Iyer, Lakin, Legge, Lo, Lockwood, Sadun, Singh, Sullivan, Tam, Turgunbaev, Reston.

Analysis and interpretation of data. Bass, Chakravarty, Akl, Bingham, Calabrese, Cappelli, Johnson, Winthrop, Arasaratnam, Baden, Berard, Bridges, Cheah, Curtis, Ferguson, Hakkarinen, Onel, Schultz, Sivaraman, Smith, Sparks, Vogel, Williams, Calabrese, Fontanarosa, Gillispie-Taylor, Gkrouzman, Legge, Lockwood, Singh, Sullivan, Tam, Turgunbaev, Reston.

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2022 American College of Rheumatology (ACR) Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases

Guideline Summary

Objective: To provide evidence-based recommendations on the use of vaccinations in children and adults with rheumatic and musculoskeletal diseases (RMDs).

Methods: This guideline follows the ACR guideline development process and ACR policy guiding management of conflicts of interest and disclosures, which includes the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology, and adheres to the Appraisal of Guidelines for REsearch & Evaluation (AGREE) criteria. A core leadership team consisting of adult and pediatric rheumatologists drafted clinical population, intervention, comparator, and outcomes (PICO) questions. A literature review team performed a systematic literature review for the PICO questions, graded the quality of evidence, and produced the evidence report. The evidence was reviewed, and recommendations were formulated by an expert Voting Panel that included adult and pediatric rheumatology providers, infectious diseases specialists, and patient representatives. Consensus required ≥70% agreement on both the direction and strength of each recommendation.

Results: This guideline includes expanded indications for some vaccines in patients with RMDs, as well as guidance on whether to hold immunosuppressive medications or delay vaccination to maximize vaccine immunogenicity. Safe approaches to the use of live-attenuated vaccines in patients on immunosuppressive medications are also addressed. The overall quality of the evidence supporting the recommendations is low, and most recommendations are conditional.

Conclusion: Application of these recommendations should take into consideration patients' individual risk for vaccine-preventable illness and for disease flares, particularly if immunosuppressive medications are held for vaccination. Shared decision-making with patients is encouraged in clinical settings.

This summary was approved by the ACR Board of Directors on July 11, 2022. These recommendations are included in a full manuscript, which will be submitted for publication in Arthritis & Rheumatology and Arthritis Care and Research.

Expanded indications for specific vaccines in patients with RMDs on immunosuppression

For RMD patients aged ≥ 65 years, and RMD patients aged >18 and <65 years who are on immunosuppressive medication, giving high-dose or adjuvanted influenza vaccination is conditionally recommended over giving regular-dose influenza vaccination.

For patients with RMD aged <65 years who are on immunosuppressive medication, pneumococcal vaccination is strongly recommended.

For patients with RMD aged >18 years who are on immunosuppressive medication, administering the recombinant zoster vaccine is strongly recommended.

For patients with RMD aged >26 and <45 years who are on immunosuppressive medication and not previously vaccinated, vaccination against HPV is conditionally recommended.

Whether to give multiple vaccinations to RMD patients on the same day

For RMD patients, giving multiple vaccinations on the same day rather than giving each individual vaccination on a different day is conditionally recommended.

Medication management at the time of non-live attenuated vaccine administration

	Influenza vaccination	Other non-live attenuated vaccinations
Methotrexate	Hold methotrexate for 2 weeks *after* vaccination*	Continue methotrexate
Rituximab	Continue rituximab**	Time vaccination for when the next rituximab dose is due, and then hold rituximab for at least 2 weeks after vaccination
Immunosuppressive medications other than methotrexate and rituximab	Continue immunosuppressive medication	Continue immunosuppressive medication

*Hold only if disease activity allows. Non-rheumatology providers, e.g., general pediatricians and internists, are encouraged to give the influenza vaccination and then consult with the patient's rheumatology provider about holding methotrexate to avoid a missed vaccination opportunity.

**Give influenza vaccination on schedule. Delay any subsequent rituximab dosing for at least 2 weeks after influenza vaccination if disease activity allows.

= Conditional recommendation

Whether to give or defer non-live attenuated vaccinations in patients taking glucocorticoids, regardless of disease activity

	Influenza vaccination	Other non-live attenuated vaccinations
Prednisone ≤ 10 mg daily*	Give	Give
Prednisone > 10 mg and < 20 mg*	Give	Give
Prednisone ≥ 20 mg daily*	Give	Defer**

*Or the equivalent dose of any other glucocorticoid formulation, or the equivalent pediatric dose

**Defer vaccination until glucocorticoids are tapered to the equivalent of prednisone < 20 mg daily

= Strong recommendation

= Conditional recommendation

For patients with RMD, giving non-live attenuated vaccinations is conditionally recommended regardless of their disease activity.

Immunosuppressive medication management at the time of live-attenuated virus vaccine administration

For RMD patients who are on immunosuppressive medication, deferring live-attenuated vaccines is conditionally recommended.

For RMD patients, holding immunosuppressive medication for an appropriate period before (see Table below) and 4 weeks after live-attenuated virus vaccination is conditionally recommended.

Immunosuppressive medication	Hold before live-attenuated virus vaccine administration	Hold after live-attenuated virus vaccine administration
Glucocorticoids[a]	4 weeks	4 weeks
Methotrexate, azathioprine[b]	4 weeks	4 weeks
Leflunomide, mycophenolate mofetil, calcineurin inhibitors, oral cyclophosphamide	4 weeks	4 weeks
JAK inhibitors	1 week	4 weeks
TNF, IL17, IL12/23, IL23, BAFF/BLyS inhibitors	1 dosing interval[c]	4 weeks
IL6 pathway inhibitors	1 dosing interval[d]	4 weeks
IL1 inhibitors		
Anakinra	1 dosing interval[d]	4 weeks
Rilonacept	1 dosing interval[d]	4 weeks
Canakinumab	1 dosing interval[d]	4 weeks
Abatacept	1 dosing interval[c]	4 weeks
Anifrolumab	1 dosing interval[c]	4 weeks
Cyclophosphamide IV	1 dosing interval[c]	4 weeks
Rituximab	6 months	4 weeks
IVIG [e]		
300-400 mg/kg	8 months	4 weeks
1 gm/kg	10 months	4 weeks
2 gm/kg	11 months	4 weeks

JAK= Janus kinase; TNF=tumor necrosis factor; IL=interleukin; IVIG= intravenous immunoglobulin G; IV = intravenous

[a] for patients taking the equivalent of prednisone < 20 mg/day or < 2 mg/kg/day for patients weighing < 10 kg, or alternate-day glucocorticoid therapy (i.e., "low level immunosuppression" (14, 68), these low doses can be continued if vaccination is critical and the risk of a disease flare or adrenal insufficiency off glucocorticoids is high.

[b] for patients taking methotrexate ≤ 0.4 mg/kg/week or azathioprine ≤ 3 mg/kg/day ("low level" immunosuppression" (14, 68), hold times can be shortened if vaccination is critical and the risk of a disease flare off immunosuppression is high.

[c] for medications with more than one FDA-approved dosing interval, the longest interval should be chosen (e.g., hold subcutaneous adalimumab for 2 weeks although it can be dosed every 1 or every 2 weeks).

[d] In children with autoinflammatory disorders or systemic juvenile idiopathic arthritis in whom the risk of disease flare if biologic DMARDs are held is very high, shorter hold times can be considered if live-attenuated vaccination is critical.

[e] the recommendation to hold IVIG prior to vaccination is designed to enhance vaccine efficacy, not safety. In some situations, such as during a measles outbreak, earlier vaccination would be preferred over delay.

When to administer live-attenuated rotavirus vaccination to infants exposed to immunosuppressive medications in utero

Antenatal drug exposure in second or third trimester	Within the first 6 months of life	After 6 months of life
TNF inhibitor	Give rotavirus vaccine	
Rituximab	Do not give rotavirus vaccine	Give rotavirus vaccine

Others

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RHEUMATOLOGY

Rheumatology 2022;61:1760–1768
https://doi.org/10.1093/rheumatology/keac115

Guidelines

GUIDELINES

British Society for Rheumatology guideline on management of paediatric, adolescent and adult patients with idiopathic inflammatory myopathy

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NICE has accredited the process used by BSR to create its clinical guidelines. The term began on 27 February 2012 and the current renewed accreditation is valid until 28 January 2023. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

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Submitted 6 July 2021; accepted 21 February 2022

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Yvonne Truepenny[35], Kishore Warrier[36], Mark Yates [9], Charalampia Papadopoulou[20], Neil Martin[37,38], Liza McCann[39,†] and Hector Chinoy [1,2,4,†], for the British Society for Rheumatology Standards, Audit and Guidelines Working Group

Key words: myositis, muscle, adolescent rheumatology, paediatric/juvenile rheumatology, DMARDs, immunosuppressants

Scope and purpose

Background

Idiopathic inflammatory myopathy (IIM) is a multi-system autoimmune condition characterised by muscle inflammation (myositis), interstitial lung disease (ILD), and skin manifestations with an incidence of up to 19 per 1,000,000 person-years in adults and up to 4 per 1,000,000 person-years in children. Estimated UK prevalence (for adult-onset IIM) is 10, 000 [1, 2].

Need for guideline

No rigorously produced evidence-based guidelines for IIM spanning juvenile and adult-onset disease exists. Assimilating key research relating to management and formation of practical evidence-based recommendations will aid clinicians and help optimize management and outcomes.

Target audience

The target readership is clinicians caring for patients with IIM, including paediatric and adult rheumatologists, neurologists, dermatologists, respiratory physicians, oncologists, gastroenterologists, and cardiologists. Rheumatology and neurology nurses, physiotherapists, occupational therapists, podiatrists, speech and language therapists, specialist rheumatology pharmacists, and psychologists will also find these recommendations relevant.

Areas the guideline does not cover

Diagnosis, classification, and investigation of suspected IIM are not addressed. Inclusion body myositis is not covered.

Stakeholder involvement

The project was led by an executive committee (J.B.L., A.G.S.O., H.C., N.M., L.M.). A multidisciplinary working group was convened with input from rheumatologists (D.I., H.G., H.T., N.Mc., A.P., P.G., S.T., H.C., P.K., P.M.M., A.G.S.O.), paediatric rheumatologists (C.Pi., C.Pa., N.Ma., K.W., L.M., T.A.), neurologists (J.B.L., M.H.), a paediatric neurologist (S.Sp.), a nurse (P.L.), a pharmacist (O.A.), a dermatologist (S.M.), paediatric dermatologist (R.M.), physiotherapists (V.C., S.M., W.J.G.), and a former GP/Specialty Doctor in Rheumatology (J.J.). Lay (patient and relative) input was also received throughout the process (P.T., Y.T., J.S., P.R.). The guideline production process was informed by a EULAR Recommended Methodologist (P.M.M.) and literature searches were carried out by experts at the Centre for Rheumatic Diseases, Kings College London (J.G., K.B., M.Y.).

Rigour of development

This guideline was developed in line with the BSR Creating Clinical Guidelines Protocol using AGREEII (Appraisal of Guidelines for Research and Evaluation II) methodology.

Selection of key questions

Starting March 2018, the executive committee and working group agreed the guideline scope and created key questions structured using the PICO (patient or population, intervention, comparison, outcome) format. Each question was subdivided into focused clinical questions during the evidence review and recommendation formulation process.

Literature search—scope and search strategy

Using key questions as a basis, a literature search was undertaken using Ovid (see 'Search terms' in Supplementary Material S1, available at *Rheumatology* online). Search results and additional manually identified references up to October 2020 were included. Evidence published after October 2020 was not included as this was the cut-off for eligibility. A potential limitation of this guideline is that relevant literature may have been published since October 2020; data or information from these studies could not be included in the recommendation formation process.

Eligibility criteria

Published peer reviewed clinical studies relating to any IIM subtype except inclusion body myositis were included. Case reports/series were limited to those describing outcomes for three or more subjects. Review articles, editorials, conference proceedings, and existing clinical guidelines were excluded. Non-English language papers were excluded unless a translation was published. Basic science studies without clear clinical applicability were excluded. Abstracts of papers were reviewed by

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two authors to determine eligibility against these criteria (PRISMA flow diagram shown in Supplementary Fig. S1, available at *Rheumatology* online).

Methods used to formulate recommendations

The full text of each eligible paper was reviewed by two assessors using Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology. Each reference was categorized as high (A), moderate (B) or low/very low (C) quality. A third assessor resolved disagreements.

A total of 213 papers were used to form recommendations. See Supplementary Table S1 (available at *Rheumatology* online) for details of evidence base contributing to recommendations.

Draft recommendations were created and categorized as applicable to all patients, adult-specific or paediatric-specific. The process outlined by the Scottish Intercollegiate Guidelines Network (SIGN) [3] was used to summarize the quality of body of evidence for each recommendation: high (A), moderate (B), low (C) or very low (D), according to GRADE methodology.

Content, wording, strength of recommendation (strong = 1, conditional = 2), and quality of supporting evidence for each recommendation were subjected to a formal consensus building process using a combination of face-to-face meetings and online surveys. Strength of agreement (SoA) for finalized recommendations was determined using a simple binary voting system for each voter and is presented as a percentage. Authors were free to abstain from voting on areas where they did not feel clinically competent, with the percentage reflecting voters. Only recommendations with a SoA >80% were included in the guideline.

Policy for updates

Requirement for updates will be considered by the BSR Standards, Audit, and Guidelines Working Group and according to principles outlined in the BSR Creating Clinical Guidelines Protocol.

Recommendations

Recommendations are followed by parentheses detailing GRADE and SoA details (strength of recommendation, quality of body of evidence, SoA).

(i) How should skeletal muscle inflammation (myositis) be treated?

1-High dose glucocorticoids should be used to treat active muscle inflammation at time of treatment induction (1, B, 100%).

1a-Adult-specific. Oral prednisolone at a dose of 0.5–1 mg/kg/day, usually 40–60 mg, is recommended (1, B, 100%).

1b-Paediatric-specific. Oral prednisolone at a dose of 1–2 mg/kg/day or intravenous methylprednisolone pulses 30 mg/kg/day, maximum 1 g daily i.v. dose is recommended (1, B, 100%).

1c-Intravenous methylprednisolone is to be considered, especially when there are concerns about gastrointestinal absorption. Use of intravenous methylprednisolone may allow increased therapeutic effect and less toxicity compared with oral glucocorticoid (2, B, 96%).

2-Oral prednisolone should be tapered according to clinical response (1, B, 100%).

3-Disease modifying anti-rheumatic drugs should be used to reduce muscle inflammation, achieve clinical remission and reduce steroid burden (1, C, 100%).

3a-Paediatric-specific. Early, complete control of muscle weakness and inflammation should be sought in juvenile-onset IIM, with the aim of improving outcomes and reducing disease-related complications (1, B, 100%).

3b-Paediatric-specific. A combination of high dose glucocorticoid and methotrexate should be used as first-line treatment in most cases (1, B, 100%).

3c-Paediatric-specific. A combination of prednisolone and methotrexate, as opposed to prednisolone and ciclosporin, should be used for the treatment of juvenile-onset IIM as this has a more favourable side effect profile (1, B, 100%).

3d-Paediatric-specific. Mycophenolate mofetil is to be considered as a treatment option to improve skin and muscle disease (2, C, 100%).

3e-Adult-specific. Methotrexate, azathioprine, tacrolimus, ciclosporin, and mycophenolate mofetil are to be considered for the treatment of active myositis and long-term maintenance of disease remission (2, C, 96%).

4-Intravenous immunoglobulin should be considered as a treatment of severe and/or refractory muscle inflammation (1, B, 100%).

5-Management of IIM should include a safe and appropriate exercise programme led and monitored by a specialist physiotherapist and/or a specialist occupational therapist to improve quality of life and function (1, B, 100%).

6-Rituximab is to be considered as a treatment option for refractory myositis and may be particularly effective in (2, A, 100%):

a. Juvenile-onset disease
b. Patients with a positive myositis autoantibody profile
c. Patients with lower burden of disease damage

7-Cyclophosphamide should be considered as a treatment option for severe and/or refractory IIM (1, B, 100%).

8-Adult-specific. Abatacept is to be considered as a treatment option in refractory adult IIM (2, B, 100%).

Glucocorticoids are crucial for myositis remission induction and maintenance. Glucocorticoid dose should be weaned when disease activity, considered across all domains, substantially improves, usually after around 6 weeks of treatment initiation. Available evidence precludes evidence-based recommendations regarding rate of glucocorticoid dose reduction. Whilst dosages per kilogram are included in recommendations for juvenile onset disease, it is important to note that ceiling doses may apply. Steroid-free remission can be facilitated

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using DMARDs and/or additional immunosuppressive/immunomodulatory treatments. Evidence exists to support use of conventional synthetic DMARDs (csDMARDs) (tacrolimus, azathioprine, methotrexate, ciclosporin, mycophenolate mofetil) alongside glucocorticoids early in the disease course to induce and maintain remission, although conflicting results exist in some cases [4–10]. Evidence does not exist to allow recommendation of specific csDMARDs as first-/second-/third-line for adults. DMARDs should be prescribed and monitored according to existing age-appropriate BSR guidelines [11, 12].

Exercise is safe and effective for people with IIM and can improve quality of life and function. Specialist physiotherapy and occupational therapy input is important for management of patients with IIM and should be considered in service planning to ensure appropriate access for all patients.

Evidence exists allowing recommendation of use of 'second-line' treatments, such as CYC, rituximab (RTX), IVIG and abatacept, for patients with persistent active disease despite glucocorticoid and csDMARD therapy. A prospective, double-blind, randomized, placebo-controlled phase III study, completed after the cut-off date for evidence inclusion, has demonstrated efficacy of IVIG [13].

CYC is an option for severe and/or refractory IIM. Route of administration should be considered since intravenous (i.v.) CYC (intermittent pulses), compared with oral CYC, is associated with fewer side effects. CYC is usually administered by i.v. infusion [14], reducing risk of leucopenia, haemorrhagic cystitis, and gonadal toxicity [15, 16].

RTX and IVIG are options for management of active IIM (e.g. myositis, dysphagia, refractory skin disease) refractory to glucocorticoid/csDMARD-based immunosuppression. In England, RTX and IVIG can only be used according to NHS England (NHSE) commissioning stipulations and should be prescribed in conjunction with a specialist centre [17, 18]. NHSE guidance does not apply in Wales, Northern Ireland or Scotland. In Scotland, the National Plasma Products Expert Advisory Group (NPPEAG) indicates IVIG as appropriate for patients with resistant or aggressive disease [19]. A single prospective delayed-start study has demonstrated the benefit of abatacept in adult-onset IIM [20]. Future studies are required to confirm efficacy.

At time of recommendation consensus forming there was insufficient evidence to recommend anti-TNF-α therapy for treatment of myositis. There was also insufficient evidence to recommend use of Janus kinase (JAK) inhibitors in IIM treatment; however, published case series are promising and future clinical trials may provide a stronger evidence base [21–23].

(ii) How should IIM-related skin manifestations be treated?

1-Rituximab is to be considered for the treatment of skin disease refractory to glucocorticoid/csDMARD-based immunosuppression (2, B, 100%).

2-IVIG should be considered for the treatment of skin disease refractory to glucocorticoid/csDMARD-based immunosuppression (1, B, 100%).

3-Sun avoidance and regular use of high factor broad spectrum sun cream is to be considered to reduce likelihood of a disease flare affecting skin or muscle (2, C, 100%).

4-**Paediatric-specific**. Systemic immunosuppressive drugs are to be considered for the treatment of ongoing skin disease activity, including reduced nailfold capillary density (2, C, 100%).

5-**Paediatric-specific**. An early increase in treatment is to be considered in patients with persistent skin disease to aid remission and reduce development of calcinosis (2, C, 100%).

Inadequate evidence exists to allow recommendation of topical agents to treat IIM-specific skin manifestations; however, topical tacrolimus and glucocorticoids could be considered alongside dermatology input.

Evidence relating to treatment of IIM-related skin manifestations is limited; however, studies indicate the ability of both IVIG and RTX to treat skin manifestations refractory to glucocorticoid/csDMARD-based immunosuppression. Nailfold capillary abnormalities in children with IIM can reflect systemic disease activity and should be considered when making treatment decisions [24].

Studies indicate sun exposure is associated with cutaneous and non-cutaneous DM and JDM disease flares [25]. Sun avoidance may thus form part of the management strategy for DM/JDM.

(iii) How should IIM-related ILD be managed?

1-**Paediatric-specific**. Routine assessment of pulmonary function, including measurement of diffusing capacity or transfer factor of the lung for carbon monoxide (DLCO or TLCO) in juvenile-onset IIM should be performed, as pulmonary function abnormalities are frequent and may be asymptomatic (1, B, 100%).

2-**Adult-specific**. Interstitial lung disease should be screened for in high-risk patients (1, B, 100%).

3-**Adult-specific**. In the treatment of rapidly progressive interstitial lung disease (RP-ILD):

a. Induction therapy with high dose steroids is to be considered (2, C, 96%).
b. The use of ciclosporin or tacrolimus, alongside steroids, is to be considered in patients with RP-ILD (2, C, 96%).
c. Cyclophosphamide or rituximab therapy is to be considered early, potentially as part of the induction regimen (2, C, 96%).

4-**Adult-specific**. In the treatment of chronic IIM-associated interstitial lung disease:

a. Immunosuppression using steroids with or without a single DMARD (azathioprine, ciclosporin, tacrolimus, mycophenolate) is to be considered (2, C, 100%).
b. Rituximab or cyclophosphamide is to be considered in treatment-resistant patients (2, C, 100%).

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IIM-related ILD management should be carried out alongside ILD-specialist respiratory physicians. ILD risk is increased with anti-synthetase syndrome, presence of an anti-synthetase-associated autoantibody, anti-melanoma differentiation-associated protein 5 autoantibody positivity, and scleroderma overlap. ILD screening methods include plain chest X-ray radiography, pulmonary function tests (including DLCO), and where indicated, high resolution CT scanning. Insufficient evidence exists to advise ILD screening frequency.

Insufficient evidence exists to form recommendations regarding pharmacological management of IIM-associated ILD in paediatric patients.

(iv) What management steps should be taken to reduce fracture risk in people with IIM?

1-Adult-specific. A bone health assessment should be performed, regardless of glucocorticoid therapy, and appropriate management instigated (1, B, 100%).

Fracture risk consideration in IIM is important given glucocorticoid use, female preponderance, and average age of onset for adult disease [26]. Fragility fracture risk assessment should be carried out in accordance with NICE guidance at time of diagnosis and whenever risk factors change [27]. Glucocorticoid weaning, once remission is attained, may reduce fragility fracture risk.

Studies, although limited by small populations, suggest JDM is associated with increased vertebral fracture risk, even before substantial corticosteroid exposure [28].

(v) What key prognostic and management factors should be considered for children with IIM?

1-Paediatric-specific. Juvenile-onset IIM should be managed by paediatric specialists as it differs from adult-onset IIM in several ways, including greater presence of subcutaneous calcification, less disease damage, lack of association with cancer, increased risk of vasculitis, and different autoantibody associations (1, C, 95%).

2-Paediatric-specific. Shorter time to diagnosis is associated with improved disease outcome, therefore early referral to a specialist service is to be considered (2, C, 100%).

3-Paediatric-specific. Age-specific considerations should be taken into account when using tools that measure muscle strength, function, and quality of life (1, B, 100%).

4-Paediatric-specific. Healthcare professionals should look for signs of connective tissue disease overlap, which is associated with increased risk of mortality (1, C, 89%).

5-Paediatric-specific. Patients with juvenile-onset IIM should be assessed for calcinosis (1, C, 100%).

Age appropriate tools such as the Childhood Myositis Assessment Score, Childhood Health Assessment Questionnaire, and Juvenile Dermatomyositis Multidimensional Assessment Report should be used to assess muscle strength, function, and quality of life [29, 30]. There is significantly higher mortality in patients with overlapping connective tissue disease features compared with those with JDM [31]. Patients should therefore be carefully screened for overlapping connective tissue disease features and wider organ involvement.

Factors associated with increased risk of calcinosis include younger age at disease onset, particularly disease onset in infancy, delay to diagnosis or delay to treatment initiation, more severe disease, prolonged disease duration, and presence of anti-nuclear matrix protein 2 (NXP2) autoantibodies [32, 33]. Clinical examination and plain X-ray radiography can be used to identify calcinosis.

(vi) Is autoantibody testing useful in people with IIM?

1-Patients should be tested for myositis auto-antibodies (1, B, 100%).

Myositis-specific antibodies and myositis-associated autoantibodies can facilitate diagnosis, inform disease phenotype and prognosis, and may help tailor treatment [34, 35]. Interpretation of immunoblot results should be carried out in the context of the patient's overall clinical presentation. Autoantibody titres should not be used to monitor disease activity.

(vii) How should cancer be screened for in people with an IIM?

1-Paediatric-specific. Routine screening for cancer is not warranted in juvenile-onset IIM (1, B, 100%).

2-Adult-specific. The risk of cancer should be considered in all patients and screening should be particularly considered in those with the following risk factors (1, B, 100%):

- Older age at onset
- Male gender
- Dysphagia
- Cutaneous necrosis
- Resistance to immunosuppressive therapy
- Rapid disease onset
- Positive anti-TIF1-γ autoantibodies
- Positive anti-NXP2 autoantibodies
- Negative for known myositis-specific autoantibodies

There is an association between adult-onset IIM and malignancy. Evidence pertaining to effective cancer screening is limited but indicates the utility of CT scanning of the thorax, abdomen, and pelvis for at-risk patients, such as anti-transcriptional intermediary factor-1γ (anti-TIF1-γ) positive patients. Tumour markers and ^{18}F-FDG PET/CT scanning can be considered in selected patients.

In contrast with adult-onset IIM, juvenile onset IIM is not associated with cancer, with literature consisting only of isolated case reports. Routine cancer screening in juvenile-onset IIM is not advised unless underlying cancer is suspected.

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(viii) How should IIM treatment during pregnancy and the breastfeeding period be amended?

1-Those wishing to conceive should be advised to plan conception whilst their disease is well controlled (1, B, 100%).

2-Pregnancy should be managed in conjunction with maternal medicine specialists (1, B, 96%).

3-Increased vigilance is required post-partum as patients may be at risk of disease flare (1, C, 96%).

Pregnancy should be managed alongside maternal medicine specialists due to lower mean birth weight, increased risk of obstetric complications, such as pre-eclampsia and eclampsia, and longer hospitalization duration during delivery. Evidence, although limited, indicates good IIM control is associated with better pregnancy outcomes [36]. Conception should be planned once disease remission is established using medications compatible with pregnancy according to the BSR guideline on prescribing drugs in pregnancy and breastfeeding [37].

(ix) How should IIM-related cardiovascular disease be assessed for and treated?

1-**Adult-specific**. Patients should undergo a regular cardiovascular risk assessment (1, C, 100%).

2-**Paediatric-specific**. Assessment and management of cardiovascular risk factors is to be considered, including hypertension, obesity or metabolic abnormalities (lipids/insulin resistance) (2, C, 100%).

IIM is associated with an increased incidence of hypertension, diabetes, dyslipidaemia, obesity, and coronary artery disease (adult-specific) representing an opportunity for intervention to reduce cardiovascular risk [38, 39]; however, insufficient evidence exists to advise screening frequency.

Micro-vasculopathy and glucocorticoid treatment are considered responsible for the hypertension observed in 25–50% of patients with JDM [40]. Studies have identified altered cardiovascular risk factors in JDM patients [41] that may lead to increased risk of early atherosclerosis later in adulthood [42].

(x) How should cardiac involvement in IIM be screened for?

1-**Adult-specific**. Patients should undergo screening for cardiac involvement; serum cardiac damage markers, ECG, echocardiography, and cardiac MRI are to be considered (2, B, 100%).

2-**Adult-specific**. Cardiac troponin I (not cardiac troponin T) should be used as the preferred serum marker for screening and monitoring cardiac involvement (1, B, 100%).

3-**Paediatric-specific**. Screening for cardiac involvement in patients with juvenile-onset IIM with ECG and echocardiogram is to be considered (2, C, 100%).

Cardiac myositis is associated with increased morbidity and mortality risk. Raised serum cardiac damage markers may indicate cardiac involvement. However, some 'cardiac-specific' markers, particularly cardiac troponin T, can also be expressed and released from regenerating skeletal muscle, potentially causing ambiguity. Measuring cardiac troponin I is recommended. Several cardiac abnormalities, including left ventricular dysfunction, ECG abnormalities, and reduced heart rate variability [43, 44], have been reported in people with IIM.

(xi) How should IIM-related dysphagia be screened for and managed?

1-Routine assessment of dysphagia is to be considered in all patients (2, C, 92%).

2-Swallowing assessment and involvement of speech and language therapist/gastroenterology teams is to be considered in those with dysphagia (2, C, 100%).

3-IVIG therapy for active disease and dysphagia resistant to other treatments is to be considered (2, C, 100%).

Dysphagia is common, impacts upon quality of life, and is associated with weight loss and aspiration pneumonia, which can be fatal. Swallowing dysfunction may not always be predicted by generalized muscle weakness [45]. Risk is increased with anti-NXP2 positivity or malignancy [46]. Clinicians should routinely enquire for dysphagia-related symptoms and consider early involvement of speech and language therapists when required.

Dysphagia is recognized as an indication for IVIG treatment by NHSE [18]. IVIG and other immunomodulatory therapies including glucocorticoid, csDMARDs (methotrexate, azathioprine, ciclosporin, tacrolimus, mycophenolate mofetil, hydroxychloroquine), CYC, and RTX have been reported to improve symptoms of dysphagia and/or objective swallow assessments.

(xii) How should quality of life and mental wellbeing be assessed and treated in people with IIM?

1-Psychological wellbeing and psychiatric comorbidities should be assessed (1, C, 92%).

2-Psychological wellbeing and health-related quality of life should be routinely assessed using an age-appropriate tool (1, B, 100%).

3-Factors negatively impacting upon health-related quality of life (e.g. skin involvement, pruritis, steroid adverse effects) should be addressed (1, C, 96%).

4-**Paediatric-specific**. Factors negatively impacting upon health-related quality of life in children include pain, muscle weakness, and poor sleep, and should be managed appropriately (1, C, 95%).

5-Individually tailored exercise and/or rehabilitation should be encouraged across all ranges of disease activity with the aim of improving psychological wellbeing (1, B, 96%).

6-Where relevant, targeted exercises given by a specialist physiotherapist and/or a specialist occupational

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therapist to improve grip strength should be considered, due to the negative impact of poor grip strength on activities of daily living and quality of life (2, C, 96%).

Significant deficits are evident in measures of health-related quality of life (HRQoL) in both adult and juvenile-onset IIM. Evidence suggests a number of IIM-specific factors that can negatively impact HRQoL, such as active disease, increased functional impairment, and decreased muscle strength [47]. HRQoL can be assessed using tools such as the Child Health Questionnaire (CHQ-50) and the 36-Item Short Form Survey (adult-specific) [48]. Minimizing functional impairment via specialist physiotherapy and/or occupational therapy should be considered. Screening for concerns such as low mood and anxiety, and offering psychological interventions as early possible where needed can be considered.

(xiii) What IIM management considerations should be made for certain ethnic groups?

1-Ethnicity is to be considered when assessing patients; clinical manifestations, associated autoantibodies, and underlying risk factors may vary according to ethnicity (2, C, 96%).

Ethnic minority groups appear to be at increased risk of anti-signal recognition particle (anti-SRP) autoantibody-related disease, increased cardiovascular risk, and more at risk of juvenile polymyositis/juvenile connective tissue myopathy. Calcinosis rates are higher in black children with JDM in North American [49] and South African cohorts [50].

Applicability and utility

Supplementary Fig. S2 (available at *Rheumatology* online) shows an overview of recommendations. There should be no barriers to implementation in the UK. Use of the audit tool (Supplementary Table S2, available at *Rheumatology* online) is encouraged.

This guideline highlights the limited high-quality evidence base available for IIM, with relative absence of RCTs or head-to-head comparison of treatments. Recommendations are therefore predominantly based on observational studies. Controlled trials are crucial to further evaluate promising treatments. Long-term outcomes especially related to cardiovascular or cerebrovascular risks needs better definition. Impact of IIM on mental health and quality of life should not be underestimated. Patients and carers should be fully integrated in defining priorities for future IIM research.

Acknowledgements

Myositis UK and JDCBS endorse the British Society for Rheumatology guideline on the management of paediatric, adolescent and adult patients with idiopathic inflammatory myopathy, which has followed NICE accredited processes in its development and production. The authors would like to thank BSR for support provided throughout each stage of formation of the guideline. The authors would also like to thank Myositis UK for funding provision that supported formation of the guideline. The authors would like to thank Dr Jennifer Hannah who took part in voting during the consensus meeting.

J.B.L., A.G.S.O., H.C., N.M. and L.M. led guideline formation throughout all stages. J.B.L., A.G.S.O., H.C., N.M., L.M. and C.Pa. prepared the guideline manuscript, which was reviewed and approved by all co-authors. J.G., K.B. and M.Y. led the systematic review process. P.T., Y.T., J.S. and P.R. provided lay (patient and relative) input throughout the process. All authors contributed to the consensus building and recommendation finalisation process and approved the final manuscript.

Funding: A.G.S.O. and H.C. are supported by the National Institute for Health Research Manchester Biomedical Research Centre Funding Scheme. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health. During production of these guidelines A.G.S.O. received salary support from Myositis UK and Versus Arthritis (Award Number: 21993); J.B.L. held an NIHR Clinical Lectureship in Neurology (NWN/006/025/A); P.L. was funded by a National Institute for Health Research (NIHR)/Health Education England (HEE) Clinical Doctoral Research Fellowship (ICA-CDRF-2016-02-032); S.L.T. held an NIHR Clinical Lectureship in Rheumatology (SEV/008/020A) funded by Royal United Hospitals NHS Foundation Trust and the Bath Institute for Rheumatic Diseases; and K.B. was funded by the Medical Research Council in the form of a Clinical Training Research Fellowship (CTRF MR/R001332/1). Support was also received from the British Society for Rheumatology to fund travel and other expenses associated with a face-to-face consensus building meeting.

Disclosure statement: All authors have made declarations of interest in line with BSR policy (see Supplementary Material, available at Rheumatology online). J.B.L. has received honoraria from Sanofi Genzyme, Biogen, and Roche. P.M.M. has received honoraria from Abbvie, BMS, Celgene, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche, and UCB. J.J. works in a unit that has received funding from Pfizer. H.C. works in a unit that has received funding from Eli Lilly, MedImmune, and Novartis; has received educational funding support from Corbus Pharmaceuticals; and has received honoraria from Argenx, Abbvie, AstraZeneca, Janssen, Orphazyme, UCB, Biogen, and Novartis. P.K. has received honoraria from Abbvie, Amgen, Eli Lilly, Gilead, Sanofi, and Sobi. W.J.G. has received educational funding support from UCB, and has received honoraria from Pfizer and Novartis. H.T. has received honoraria from Eli Lilly, Abbvie, Janssen, Novartis, Biogen, and UCB. All other authors have declared no conflicts of interest.

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Data availability statement

All relevant data produced during the guideline development process are presented in this manuscript or in the accompanying supplementary material.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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EXTENDED REPORT

EULAR revised recommendations for the management of fibromyalgia

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Handling editor Tore K Kvien

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2016-209724).

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Received 15 April 2016
Revised 10 June 2016
Accepted 14 June 2016
Published Online First 4 July 2016

ABSTRACT

Objective The original European League Against Rheumatism recommendations for managing fibromyalgia assessed evidence up to 2005. The paucity of studies meant that most recommendations were 'expert opinion'.

Methods A multidisciplinary group from 12 countries assessed evidence with a focus on systematic reviews and meta-analyses concerned with pharmacological/non-pharmacological management for fibromyalgia. A review, in May 2015, identified eligible publications and key outcomes assessed were pain, fatigue, sleep and daily functioning. The Grading of Recommendations Assessment, Development and Evaluation system was used for making recommendations.

Results 2979 titles were identified: from these 275 full papers were selected for review and 107 reviews (and/or meta-analyses) evaluated as eligible. Based on meta-analyses, the only 'strong for' therapy-based recommendation in the guidelines was exercise. Based on expert opinion, a graduated approach, the following four main stages are suggested underpinned by shared decision-making with patients. Initial management should involve patient education and focus on non-pharmacological therapies. In case of non-response, further therapies (all of which were evaluated as 'weak for' based on meta-analyses) should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation programme (for severe disability).

Conclusions These recommendations are underpinned by high-quality reviews and meta-analyses. The size of effect for most treatments is relatively modest. We propose research priorities clarifying who will benefit from specific interventions, their effect in combination and organisation of healthcare systems to optimise outcome.

INTRODUCTION

Fibromyalgia is common with a prevalence of 2% in the general population.[1 2] However, its diagnosis and management remain a challenge for patients and healthcare professionals. It often takes >2 years for a diagnosis to be made with an average of 3.7 consultations with different physicians.[3] Referral to specialists and investigations results in high healthcare use, for up to 10 years prior to diagnosis, compared with persons who do not have fibromyalgia.[4] Although pain is the dominant symptom in fibromyalgia, other symptoms such as fatigue, non-refreshed sleep, mood disturbance and cognitive impairment are common, but not universal, have an important influence on quality of life and emphasise that it is a heterogeneous and complex condition.[5 6]

The original European League Against Rheumatism (EULAR) recommendations for the management of fibromyalgia assessed evidence up to and including 2005.[7] Given the paucity of information and poor quality of the studies available, it was recommended that the guidelines be revised after a period of 4 years. However, no subsequent revision took place and thus a decade later we revisit the recommendations with the aim of making them more evidence based. In the time since the original recommendations, there have been a considerable number of individual trials examining pharmacological and non-pharmacological interventions and, moreover, there have been systematic reviews conducted for nearly all of the commonly used management strategies. Our aim therefore was, using the systematic reviews conducted and taking into account their quality, to make evidence-based recommendations for the use of individual pharmacological and non-pharmacological approaches, and how these could be combined. Further, we aimed to identify priority areas for future research.

METHODS

Working group membership

The working group included 18 members from 12 European countries: clinicians (representing rheumatology, internal medicine, pain medicine and epidemiology), non-clinical scientists (occupational health, epidemiology), patient representatives and the allied health professions (nursing).

Eligibility, search strategy and quality assessment

We focused on systematic reviews (with or without meta-analysis) concerned with the management of fibromyalgia. Details of eligibility, review and quality assessment are provided in online supplementary text.

Evaluating evidence

We retained pain as one of the key outcomes of interest, from the original guidelines, but also included fatigue, sleep and daily functioning. The committee considered the following in making a

To cite: Macfarlane GJ, Kronisch C, Dean LE, *et al*. *Ann Rheum Dis* 2017;**76**:318–328.

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recommendation: number of trials, number of patients, outcomes assessed, quality of reviews and the trials included within the reviews, effect size (and 95% CI), adverse events and cost. We used the Grading of Recommendations Assessment, Development and Evaluation system for making recommendations.[10] This is a four-point scale: strong for/weak for/weak against/strong against; or allowing a recommendation 'use only for research'. The strength of recommendation is based on the balance between desirable and undesirable effects (considering values and preferences), confidence in the magnitude of effects and resource use. A strong recommendation implies that, if presented with the evidence, all or almost all informed persons would make the recommendation for or against the therapy, while a weak recommendation would imply that most people would, although a substantial minority would not.[11]

Two subgroups considered the evidence for pharmacological and non-pharmacological therapies and proposed a recommendation. At a face-to-face meeting, after presentation of the evidence and the preliminary recommendation, discussion resulted in a 'final recommendation'. In addition to the evidence on efficacy/effectiveness, the committee also took into account safety. All participants then voted on their level of agreement with the recommendation on a scale from 0, 'completely disagree', to 10, 'completely agree'. The percentage of the committee scoring at least 7 was taken to indicate level of agreement.

RESULTS

In total, 2979 titles were identified. From these, 571 abstracts and then 275 full papers were selected for review, and 107 reviews evaluated as eligible for consideration in making recommendations for management (figure 1).

Information on the reviews informing these recommendations on pharmacological therapy and on non-pharmacological and complementary and alternative medicines/therapies is collated in online supplementary tables A and B, respectively, while information from one review, for each medicine/therapy, selected based on recency and quality is provided in tables 1 and 2, respectively.

Evaluation of pharmacological medicines

Amitriptyline

Five reviews included up to 13 trials and a maximum of 919 subjects. Häuser *et al*[12] reported that patients receiving amitriptyline were more likely to achieve 30% pain reduction (risk ratio (RR) 1.60, 95% CI 1.15 to 2.24), equivalent to a 'number needed to treat' (NNT) of 3.54, 95% CI 2.74 to 5.01. There was a moderate effect on sleep (standardised mean difference (SMD) −0.56, 95% CI −0.78, to −0.34)[i] and small effect on fatigue (−0.44; −0.71 to −0.16). There was no difference in discontinuation rates compared with patients receiving placebo. Nishishinya *et al*[13] in their high-quality review concluded that 25 mg/day improved pain, sleep and fatigue at 6–8 weeks of treatment but not at 12 weeks while 50 mg/day did not demonstrate efficacy. *Amitriptyline evaluation: weak for, at low dose (100% agreement).*

Anticonvulsants

Nine reviews of pregabalin included up to seven studies and a maximum of 3344 patients. A recent Cochrane review[24] reported patients receiving active treatment were more likely to have 30% pain reduction, RR 1.37, 95% CI 1.22 to 1.53, with a 'number needed to benefit' (NNTB) over placebo of 9, 95% CI 7 to 13. There was a very small effect on fatigue (−0.17; −0.25 to −0.09) and small effect on sleep (−0.35; −0.43 to −0.27) but no effect on disability (−0.01; −0.11 to 0.09). A single, moderate quality, study of gabapentin in 150 subjects (eg, in ref. 104) showed a significant effect on 30% pain reduction (RR 1.65, 95% CI 1.10 to 2.48), a small effect on sleep (−0.71; −1.08 to −0.24) and a large effect on disability (−0.94; −1.32 to −0.56). *Anticonvulsant evaluation: pregabalin—weak for (94% agreement); gabapentin—research only (100% agreement).*

Cyclobenzaprine

A single systematic review of five studies involving 312 patients reported that of those taking cyclobenzaprine 85% experienced side effects and only 71% completed the studies. They were more likely to report themselves as 'improved' (NNT 4.8, 95% CI 3.0 to 11.0). Only two studies reported an 'intention-to-treat' (ITT) analysis. Sleep, but not pain, showed a significant, very small, improvement relative to baseline at the longest outcome considered (12 weeks: SMD 0.34) and patients on placebo showed similar improvement (SMD 0.52).[25] *Cyclobenzaprine evaluation: weak for (75% agreement).*

Growth hormone

A single systematic review of two studies involving 74 patients reported an effect size on pain of 1.36 (0.01 to 1.34).[16] The improvement in functional deficit was not statistically significant (1.24; −0.36 to 2.84). There are concerns on safety (sleep apnoea, carpal tunnel syndrome). The drug is not approved for fibromyalgia (FM) or related disorders in Europe. *Growth hormone evaluation: strong against (94% agreement).*

Monoamine oxidase inhibitors

Four reviews identified up to three studies and 241 patients. Häuser *et al*[26] reported a moderate effect on pain across the studies (−0.54; −1.02, to −0.07), but the single studies that evaluated fatigue and sleep showed no effect. There were no differences in dropouts or adverse events compared with placebo. There was no comparison between compounds. Life-threatening interactions have been documented. *Monoamine oxidase inhibitors (MAOIs) evaluation: weak against (81% agreement).*

NSAIDs

A single review[21] identified two small trials with no evidence of improved outcome compared with placebo. One low-quality review was not considered. *Non-steroidal anti-inflammatory drugs (NSAIDs) evaluation: weak against (100% agreement).*

Serotonin-noradrenalin reuptake inhibitors

Eight systematic reviews were identified, which presented data separately for duloxetine. The largest review of 2249 subjects[32] reported duloxetine, short term (up to 12 weeks) and long term (up to 28 weeks), was more effective than placebo at reducing pain (RR >30% pain, RR 1.38, 95% CI 1.22 to 1.56), although there was no significant effect at 20–30 mg/day and no difference between doses of 60 and 120 mg/day. NNTB, based on 60 mg/day up to 12 weeks, was 6, 95% CI 3 to 12. A previous review reported small effects on sleep (−0.24; −0.37, to −0.12) and disability (−0.33; −0.43, to −0.24) but no effect on fatigue.[30] Seven systematic reviews were identified of milnacipran, a recent one of which evaluated five trials.[30] Patients taking milnacipran were more likely, at the end of treatment, to

[i]All effect sizes are expressed as SMD with 95% CI unless otherwise stated.

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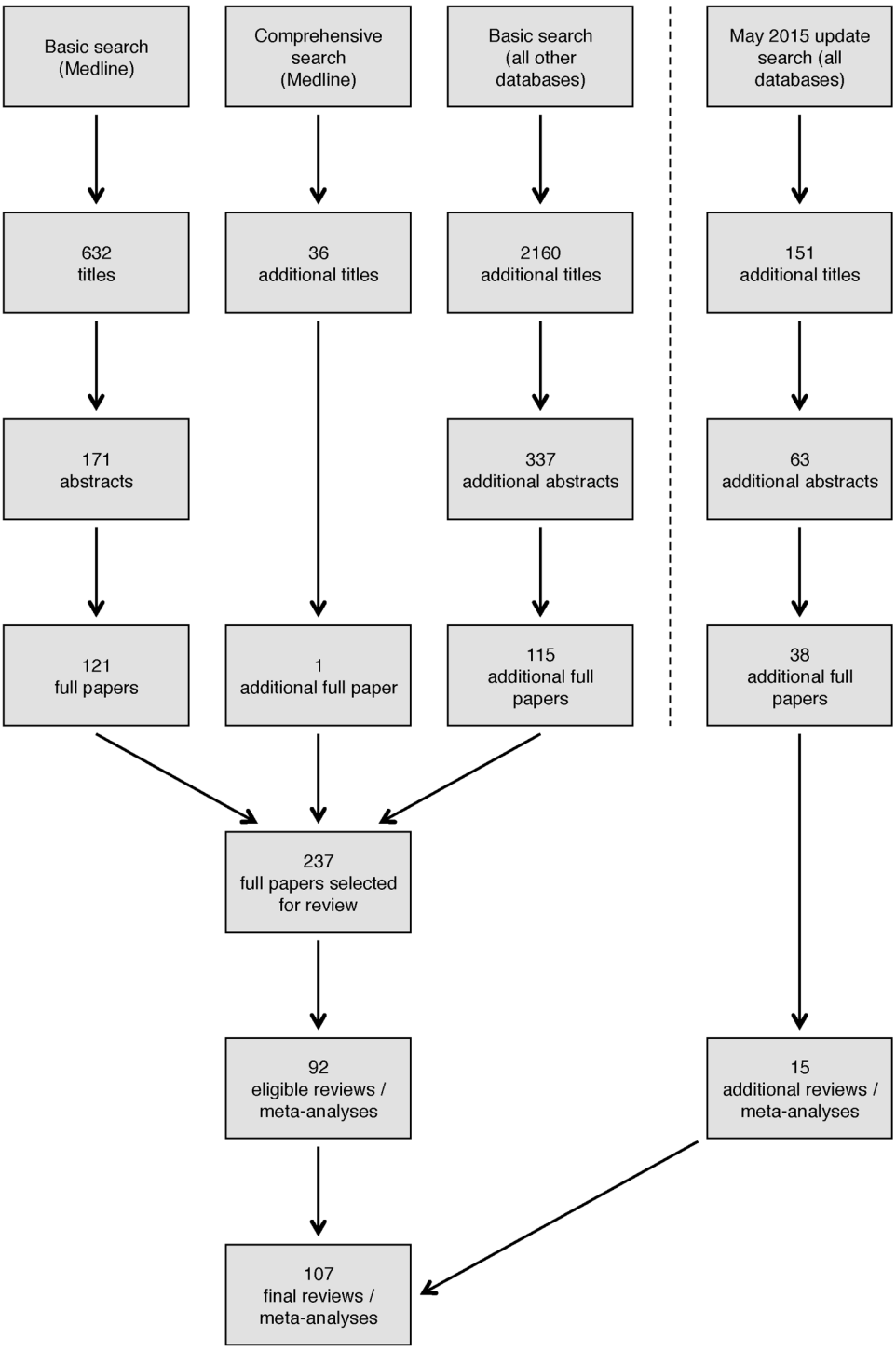

Figure 1 Flow chart identifying eligible reviews.

have 30% pain reduction (RR 1.38, 95% CI 1.25 to 1.51) but there was only a small benefit on fatigue (−0.14; −0.19 to −0.08), disability (−0.16; −0.23 to −0.10) and no effect on sleep. *Duloxetine and milnacipran evaluation: weak for (100% agreement).*

Selective serotonin reuptake inhibitors

Seven systematic reviews included up to 11 trials and a maximum of 521 subjects. Given that reviews have not focused on specific drugs or comparisons, drugs within this class were considered together. A recent review of medium quality included seven trials and reported a moderate effect on pain (−0.40; −0.73, to −0.07), sleep (−0.31; −0.60 to −0.02) and no effect on fatigue (−0.17; −0.46 to 0.11).[36] *Selective serotonin reuptake inhibitor (SSRI) evaluation: weak against (94% agreement).*

Sodium oxybate

A single systematic review of five studies including 1535 patients reported small effects sizes on pain (0.44; 0.31 to 0.58), sleep problems (0.47; 0.28 to 0.66) and fatigue (0.48; 0.35 to 0.60). The European Medicines Agency and the US Food and Drug Administration refused the approval for FM because of safety concerns.[16] The drug is only approved for narcolepsy. *Sodium oxybate evaluation: strong against (94% agreement).*

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Table 1 Overview of results from selected systematic reviews of placebo-controlled pharmacological trials

Treatment (review reference)	No. of trials (no. of participants) Review quality	Dosages; durations of treatment	Overall trial quality*	Safety and comments
Amitriptyline[12]	10 (767) AMSTAR=6	10–50 mg/day; 8–24 weeks	Low	There was no analysis of safety but no difference in discontinuation rates compared with patients on placebo was reported.
Anticonvulsants—pregabalin[24]	5 (3256) AMSTAR=10	Three studies with fixed doses of 300, 450 and 600 mg/day; one with fixed doses of 150, 300 or 450 mg/day; one flexible dosing study of 300 or 450 mg/day; 8–14 weeks	High	Increased likelihood of withdrawal due to adverse events, RR 1.68, 95% CI 1.36 to 2.07; NNH 12 95% CI 9 to 17. No difference in likelihood of serious adverse events.
Cyclobenzaprine[25]	5 (312) AMSTAR=7	10–40 mg; 2–24 weeks	Moderate	There was no analysis of adverse outcomes in the trials reviewed although dropout across trials was large (cyclobenzaprine 29%, placebo 43%). Only two studies conducted ITT.
Growth hormone[16]	2 (74) AMSTAR=5	0.0125 mg/kg/day; adjusted to maintain IGF-1 level of 250 ng/mL after first month, 0.0125 mg/kg/day; 9 months to 1 year	NE	Safety concerns include sleep apnoea and carpal tunnel syndrome.
MAOIs[26]	3 (241) AMSTAR=9	Pirlindole 150 mg/day, moclobemide 150–300 mg/day; 4–12 weeks	Low	MAOIs are known to cause potentially fatal hypertensive crises, serotonin syndrome and psychosis when they interact with foods containing tyramine and medications (many of which are commonly used in the treatment of FM), including SSRIs, tricyclic antidepressants and tramadol. The clinical trials had restrictions on concomitant medications.
NSAIDs[21]	2 (242) AMSTAR=7	Ibuprofen 600 mg four times a day, tenoxicam 20 mg/day; 6–8 weeks	Low	The adverse event profile, although not considered in this review, is well established for this class of drugs.
SNRIs—duloxetine[31]	6 (2249) AMSTAR=10	20–120 mg/day; 12–28 weeks	Moderate	Dropout rates due to side effects across studies higher than with placebo. No difference in serious adverse events.
SNRIs—milnacipran[30]	5 (4118) AMSTAR=10	100 or 200 mg/day; 12–27 weeks	High	Dropout rates due to side effects across studies were double compared with placebo, but there was no difference in serious adverse events.
SSRIs[36]	7 (322) AMSTAR=8	20–40 mg/day citalopram, 20–80 mg/day fluoxetine, 20–60 mg/day paroxetine; 6–16 weeks	Moderate to high	Acceptability and tolerability were similar to placebo NNH 40, 95% CI 19 to 66. Although several studies excluded patients with depression/anxiety, Häuser *et al*[26] showed a small effect of SSRIs in improving depressed mood (SMD −0.37, 95% CI −0.66 to −0.07).
Sodium oxybate[16]	5 (1535) AMSTAR=5	4.5–6 g/day; 8–14 weeks	NE	There is the potential for abuse and central nervous system effects associated with abuse such as seizure, respiratory depression and decreased levels of consciousness.
Tramadol[22]	1 (313) AMSTAR=3	37.5 mg tramadol/325 mg paracetamol 4×/day; 3 months	High	No significant difference in discontinuation due to adverse events (RR 1.62, 95% CI 0.94 to 2.80). A high-quality review (AMSTAR score 7) identified a single study, which, among persons who tolerated and benefitted from tramadol, demonstrated a lower discontinuation rate in a double-blind phase compared with placebo.[21]

*According to the method of quality evaluation used in the review.
AMSTAR, Assessing the Methodological Quality of Systematic Reviews; FM, fibromyalgia; IGF, insulin growth factor; ITT, intention-to-treat; MAOIs, monoamine oxidase inhibitors; NE, not evaluated; NNH, number needed to harm; NSAIDs, non-steroidal anti-inflammatory drugs; RR, risk ratio; SMD, standardised mean difference; SNRI, serotonin-noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Tramadol, a weak opioid with mild serotonin-noradrenalin reuptake inhibitor (SNRI) activity was considered by two reviews. Roskell *et al*[22] identified a single study of tramadol with paracetamol. Those in the active arm were more likely to have 30% improvement in pain (RR 1.77, 95% CI 1.26 to 2.48). *Tramadol evaluation: weak for (100% agreement)*.

The literature search did not identify any reviews on corticosteroids, strong opioids, cannabinoids and antipsychotics. The committee made a 'strong against' evaluation (100% agreement) regarding the use of strong opioids and corticosteroids in patients with fibromyalgia on the basis of lack of evidence of efficacy and high risk of side effects/addiction reported in individual trials.

Evaluation of non-pharmacological therapies; complementary and alternative medicines and therapies

Acupuncture

Eight reviews included up to 16 trials and 1081 participants. One high-quality review included nine trials, with 395 patients, and demonstrated that acupuncture, added to standard therapy, resulted in a 30% (21%, 39%) improvement in pain.[70] Electric acupuncture was also associated with improvements in pain (22%; 4% to 41%) and fatigue (11%; 2% to 20%). Some adverse events were reported, but these were commonly mild and transient. There is little understanding of the active component of acupuncture, and the evidence supporting the use of real versus sham acupuncture was less consistent. *Acupuncture evaluation: weak for (93% agreement)*.

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Table 2 Overview of results from selected systematic reviews of non-pharmacological; complementary and alternative medicine and therapy trials

Treatment (review reference)	No. of trials (no. of participants*) Review quality	Dosages; durations of treatment	Overall trial quality†	Safety and comments
Acupuncture[70]	9 (395) AMSTAR=11	Treatment sessions ranged from 3 to 13 weeks (median=4), with needle retention ranging from 20 to 30 min. Only one study provided journal references for the acupuncture point selection, and the description of the type of needle stimulation/ manipulation was clear in only three studies.	Moderate	One in six people who had acupuncture, and one in three controls, reported adverse events. Such events were minor and lasted less than one day. No serious adverse events were reported in any trials.
Biofeedback[92]	7 (321) AMSTAR=8	EMG biofeedback. Individual sessions varied between 45 and 180 min, and the number of sessions varied between 6 and 16. EEG biofeedback. 20–22 sessions of (where reported) 30 min duration.	Poor	Only two‡ trials reported adverse event data. 4% of patients in one trial receiving EMG biofeedback reported stress. And 74% of patients in another, receiving EEG biofeedback reported a variety of side effects, including: headache, fatigue and sleep problems.
Capsaicin[94]	2 (153) AMSTAR=5	Topical application of *Capsicum annuum L*. cream, either 0.025% capsaicin for 4 weeks or 0.075% for 12 weeks.	Not reported	Patients reported moderate, transient, burning or stinging.
Chiropractic[89]	3 (102) AMSTAR=4	Little detail is given for any trials, but treatment elements included massage, stretching, spinal manipulation, education and resistance training.	Low	Around 50% of patients experience mild-to-moderate transient adverse effects after spinal manipulation.§
CBT[57]	23 (2031) AMSTAR=11	Median duration of therapy=10 weeks, with a median number of 10 sessions, and median total hours=18 hours. All but two studies delivered therapy face to face. Median follow-up (where this was performed 17/23 studies)=6 months.	Low	The assessment of safety in most studies was insufficient. Two studies reported dropout due to worsening of comorbid mental disorders. However, CBT is generally considered safe.
Exercise[41]	34 (2276) AMSTAR=9	Exercise programmes lasting 2.5–24 weeks. Aerobic exercise for ≥20 min, once a day (or twice for ≥10 min), 2–3 days a week. Strength training with ≥8 repetitions per exercise, 2–3 times a week.	Moderate	Although patients may initially notice a deterioration in symptoms, exercise is generally considered safe, especially when practised under supervision.
Hydrotherapy/spa therapy[76]	10 (446) AMSTAR=9	Wide variation in precise treatment strategy between trials. Most consisted of water or mud baths at body temperature 36–37°C, or slightly above (40–45°C), with a median treatment time of 240 min (range 200–300), over several weeks.	Low	Three studies reported no side effects of treatment; one reported slight flashes in 10% of the patients. The remaining trials did not explicitly mention safety.
Hypnotherapy[91]	4 (152) AMSTAR=11	Some variation between trials ranging (where reported) from 300 to 420 min, delivered over 10–26 weeks.	Good	Adverse events were not reported in any of the trials.
Massage[63]	9 (404) AMSTAR=7	Massage therapy time lasted 25–90 min, with between 1 and 20 massage sessions in total.	Low to moderate	No adverse events were reported in any of the trials.
Meditative movement[80]	7 (362) AMSTAR=9	Wide variation in treatments between trials, and included yoga, tai chi, qigong or body awareness therapy. Median (range) duration of treatment=16 (6–24) hours, over 4–12 weeks.	Moderate	Although no serious adverse events were reported, six participants (3.1%) withdrew from the trials because of adverse events (increase of pain; muscle inflammation; chlorine hypersensitivity). The review authors concluded that the acceptance and safety of all types of meditative movement therapies were high.
Mindfulness/mind–body therapy[84]	6 (674) AMSTAR=9	Some variation between trials. Single 2–3.5 hours session per week, for 8–10 weeks. Four out of six programmes also included daily home practice (30–45 min) plus a single all-day retreat.	Low	Safety was assessed and reported in none of the trials.
Multicomponent therapy[60]	9 (1119) AMSTAR=9	Enormous variation in treatment strategies between trials. Most included different combinations of exercise (land and/or water based); education; relaxation; and/or some other specific therapeutic component (eg, Tai Chi; or massage).	Moderate	No adverse events were reported in any of the trials.
SAMe[93]	1 (44) AMSTAR=6	400 mg tablet, twice a day, for 6 weeks.	Moderate	Mild adverse effects such as stomach upset and dizziness were reported.
Other: guided imagery[91]	1 (48) AMSTAR=9	Audiotape-led, individual, guided imagery: 30 min daily for 6 weeks recommended. Median of 44 exercises (range 37–136).	Good	Adverse events were not reported.
Other: homeopathy[98]	4 (163) AMSTAR=7	Variation between trials. Two studied individualised homeopathic treatment, consisting of an initial consultation (and treatment), plus follow-up interviews every 4–8 weeks. Two studied *Arnica montana*, *Bryonia alba* or *Rhus toxicodendron* (potency 6c) daily for between 1 and 3 months.	Low to moderate	No information was provided on safety.

*Total number of persons randomised.
†According to the method of quality evaluation used in the review.
‡Elsewhere in the review, it reports that three studies reported on adverse events. However, in the table where these data are presented, it is only clear for two. However, in a third trial, there were no dropouts due to side effects.
§These data were not contained in this review. The initial recommendation for chiropractic was weak against. However, after discussion, this was downgraded to strong against due to potential safety concerns.
CBT, cognitive behavioural therapy; EMG, electromyographic; SAMe, *S*-adenosyl methionine.

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Biofeedback

Two reviews included up to seven trials and 307 participants. Glombiewski *et al*[92] reviewed seven studies, comprising 321 participants. Treatment sessions varied from 6 to 22; with control therapy comprising sham biofeedback, attention control, medication and treatment as usual. Biofeedback was effective in reducing pain intensity (Hedges' g=0.79; 0.22 to 1.36), although all trials were poor quality. There was no evidence of effectiveness in terms of fatigue or sleep and subgroup analysis suggested that any effect was limited to electromyographic (0.86; 0.11 to 1.62) rather than electroencephalographic biofeedback (0.71; −0.37 to 1.8). *Biofeedback evaluation: weak against (100% agreement).*

Capsaicin

Two reviews included two trials and 153 participants. The most recent review, a narrative review of two trials, considered data on 153 patients.[94] Both showed some evidence of positive effect in terms of pain relief, although results were not consistent for other outcomes. Capsaicin gel is generally considered safe, although many users report a mild burning sensation when applied to the skin. However, the number of patients and trials was small and was therefore limited in the extent to which they can provide evidence for toxicity. *Capsaicin evaluation: weak against (86% agreement).*

Chiropractic

Three reviews included up to 13 trials and 102 participants. The most recent review summarised three studies.[89] One study was an open pilot study, one quasi-randomised and in the third no between-group differences were observed in terms of pain. The studies were poor quality and lacked robust interpretable data. *Chiropractic evaluation: strong against (93% agreement).*

Cognitive behavioural therapies

Five reviews included up to 30 trials and at least 2031 participants. One high-quality review included 23 trials, comprising >2000 patients, although the quality of individual trials was reported as generally poor.[58] Cognitive behavioural therapies (CBTs) were effective in reducing pain (−0.29; −0.49 to −0.17) and disability (−0.30; −0.51 to −0.08) at the end of treatment compared with a variety of controls groups, and results were sustained long term. *Behavioural therapy evaluation: weak for (100% agreement).*

Exercise

Twenty reviews included up to 34 trials and at least 2494 participants.[ii] The largest, a Cochrane review, considered 47 different exercise interventions.[41] Aerobic exercise was associated with improvements in pain (0.65; −0.09 to 1.39) and physical function (0.66; 0.41 to 0.92). Busch *et al*[42] reviewed five trials with 219 participants and concluded that resistance training resulted in a significant improvement in pain (−3.3 cm on a 10 cm scale; −6.35 to −0.26) as well as function compared with control. There is some consistency with regard to aerobic and strengthening exercises, although insufficient evidence to suggest superiority of one over the other; land and aquatic exercise appear equally effective.[56] *Exercise therapy evaluation: strong for (100% agreement).*

[ii]It is unclear from some of the reviews how many participants were included. The number of participants represents the minimum about which we can be confident.

Hydrotherapy/spa therapy

Four reviews included up to 21 trials and 1306 participants. One high-quality review included 10 trials, 446 participants and compared a median of 4-hour hydrotherapy (range 200–300 min) against various comparators.[76] There was a significant improvement in pain (−0.78; −1.42 to −0.13) at the end of therapy, maintained in the longer term (median 14 weeks), although the review authors noted that no trials conducted an ITT analysis. There was consistency with regard to the evidence for hydrotherapy and balneotherapy, although little evidence to suggest superiority of one over the other.[77] *Hydrotherapy evaluation: weak for (93% agreement).*

Hypnotherapy

One review included four trials, although the number of participants is unclear.[91] Although six trials of hypnotherapy and/or guided imagery were reviewed, only four examined hypnotherapy in isolation. Median treatment duration (where reported) was 360 min and hypnotherapy was compared with a variety of control therapies: cognitive intervention, active control (physical therapy/massage/relaxation/autogenic training) and treatment as usual. A meta-analysis is presented on all six trials, and isolated data for hypnotherapy are not presented. Two of the four hypnotherapy trials report some significant benefit in terms of pain, the other two demonstrate null, non-significant results. *Hypnotherapy evaluation: weak against (86% agreement).*

Massage

Six reviews have been reported and one meta-analysis with nine trials and 404 patients[63] with sessions lasting 25–90 min, and treatment duration ranging from 1 to 24 weeks (median 5 weeks). Comparator treatments included transcutaneous electrical nerve stimulation (TENS), standard care, guided relaxation and acupuncture. Methodological problems were noted with all of the studies, only four were at low risk of bias in terms of random allocation and only two were analysed as ITT. Overall, massage was not associated with a significant improvement in pain (0.37; −0.19 to 0.93), and of the two ITT analyses, one favoured massage and one favoured control (both significant). A subgroup analysis revealed some evidence of a positive effect with massage of ≥5 weeks duration, although this was based solely on lower-quality trials. *Massage evaluation: weak against (86% agreement).*

Meditative movement

Six reviews, including up to eight trials and 559 participants, focused on qigong, yoga, tai chi or a combination of these therapies. However, there was insufficient evidence to make individual recommendations. One review included seven trials, with 362 participants randomised to tai chi, yoga, qigong or body awareness therapy.[80] Total treatment time ranged from 12 to 24 hours and was compared with a variety of controls, including treatment as usual and active control groups (aerobics, wellness education and stretching). At the end of therapy, improvements were seen in sleep (−0.61; −0.95 to −0.27) and fatigue (−0.66; −0.99 to −0.34) some of which were maintained in the longer term. *Meditative movement evaluation: weak for (71% agreement).*

Mindfulness/mind–body therapy

Six reviews included up to 13 trials and 1209 participants. One recent review, a meta-analysis of six trials, with 674 patients[84] provided evidence that mindfulness-based stress reduction

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resulted in improvements in pain (−0.23; −0.46 to −0.01) immediately post treatment compared with usual care and compared with active control interventions (−0.44; −0.73 to −0.16). However, these effects were not robust against bias. *Mindfulness/mind–body therapy evaluation*: *weak for (73% agreement)*.

Multicomponent therapy

Two reviews including up to 27 trials and 2407 participants examined the additional benefit of combining therapies compared with individual therapy. Häuser *et al*[60] conducted a review of management involving both educational or psychological therapies and exercise. In a meta-analysis of nine trials and 1119 patients, multicomponent therapy was effective in reducing pain (−0.37; −0.62 to −0.13), and fatigue, immediately post treatment, compared with waiting list, relaxation, treatment as usual and education. However, effects were short-lived. *Multicomponent therapy evaluation: weak for (93% agreement)*.

S-Adenosyl methionine

Two reviews each included one trial with, in combination, 74 participants. De Silva *et al*[93] reported that, after the end of treatment, significant improvements were observed in pain and fatigue compared with placebo. Sim and Adams[52] reviewed a trial comparing *S*-adenosyl methionine (SAMe) with TENS but data on the main trial comparison are omitted. Side effects are usually mild and infrequent. However, the number of patients and trials was small and therefore cannot provide a robust assessment of toxicity and safety. *SAMe evaluation: weak against (93% agreement)*.

Other complementary and alternative therapies

Three reviews of guided imagery included up to six trials and 357 participants. The highest quality, including only one trial, provided some evidence that guided imagery may be effective in reducing pain (−1.52; −2.17 to −0.87).[90] Two reviews of homeopathy included four trials and 163 participants.[97 98] Both contained a review including only four randomised trials, each of which showed some benefit of homeopathy, on some outcomes. However, none of the individual trials were without serious flaws. *Other complementary and alternative therapies (guided imagery, homeopathy): strong against (93% agreement)*.

Reviews were identified that examined electrothermal and phototherapeutic therapy;[99] phytothermotherapy;[100] music therapy, journaling/storytelling[103] and static magnet therapy,[101] although each was insufficient to allow a recommendation. Marlow *et al*[102] examined the effectiveness of transcranial magnetic and/or direct current stimulation. Eight trials included 244 participants, although not all were analysed by ITT, and appropriate group comparisons were not presented for all studies. Overall, there was little evidence to support either therapy, and several studies reported an unacceptably high rate of adverse events and/or discontinuation due to headache.

EULAR revised recommendations

In terms of overall principles, we recommend, based on unanimous expert opinion, that optimal management requires prompt diagnosis and providing the patient with information (including written material) about the condition. There should be a comprehensive assessment of pain, function and the psychosocial context. Management should take the form of a graduated approach with the aim of improving health-related quality of life. It should focus first on non-pharmacological modalities. This is based on availability, cost, safety issues and patient preference.

We have used the evaluation of individual therapies (above) to make 10 specific recommendations, all based on evidence from systematic reviews and all but one from meta-analysis. The recommendations are given in table 3, and a flow chart of how these therapies may be used in management is shown in figure 2.

We were unanimous in providing a 'strong for' recommendation for the use of exercise, particularly given its effect on pain, physical function and well-being, availability, relatively low cost and lack of safety concerns. The available evidence did not allow us to distinguish between the benefits of aerobic or strengthening. We gave 'weak for' recommendations in relation to meditative movement therapies (which improved sleep, fatigue and quality of life) or mindfulness-based stress reduction (which improved pain and quality of life); the physical therapies acupuncture or hydrotherapy for which there was evidence that they improved pain/fatigue and pain/quality of life, respectively. The effects seen in pragmatic trials of such therapies will include specific and non-specific effects, and it is not possible to disentangle these. There were some non-pharmacological therapies we did not recommend because of lack of effectiveness and/or low study quality: biofeedback, capsaicin, hypnotherapy, massage, SAMe and other complementary and alternative therapies. We provided a 'strong against' evaluation for chiropractic based on safety concerns.

In case of lack of effect of the above therapeutic approaches, we recommend individualised treatment according to patient need. Psychological therapies ('weak for') should be considered for those with mood disorder or unhelpful coping strategies: CBT was effective at producing modest, long-term reductions in pain, disability and improving mood. Pharmacological therapies (all 'weak for') should be considered for those with severe pain (duloxetine, pregabalin, tramadol) or sleep disturbance (amitriptyline, cyclobenzaprine, pregabalin). Multimodal rehabilitation ('weak for') programmes should be considered for those with severe disability—in comparison to individual therapies, those that were multimodal improved a range of short-term outcomes. We did not recommend several pharmacological therapies including NSAIDs, MAOIs and SSRIs because of lack of efficacy and specifically gave a 'strong against' evaluation to growth hormone, sodium oxybate, strong opioids and corticosteroids based on lack of efficacy and high risk of side effects.

DISCUSSION

The previous EULAR recommendations provided an important milestone in the management of fibromyalgia. There were nine recommendations, but only three were supported by strong evidence from the scientific literature; most were based on expert opinion. Since that time, there have been a considerable number of trials published addressing issues in the management of fibromyalgia. The availability of systematic reviews and meta-analysis of randomised controlled trials (RCTs) for all the most common approaches to management allowed us to concentrate on these.

Comparison with 2007 EULAR recommendations

Despite the very large increase in the amount of trial data and summarised in meta-analyses, there are no major changes to the approach of managing patients with fibromyalgia, although we provide new evidence in support for some additional non-pharmacological therapies. In addition, all the recommendations are now firmly evidence based. We now recommend that non-pharmacological therapy should be first-line therapy and then if there is a lack of effect that there should be individualised

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Table 3 Recommendations

Recommendation	Level of evidence	Grade	Strength of recommendation	Agreement (%)*
Overarching principles				
Optimal management requires prompt diagnosis. Full understanding of fibromyalgia requires comprehensive assessment of pain, function and psychosocial context. It should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features. In general, the management of FM should take the form of a graduated approach.	IV	D		100
Management of fibromyalgia should aim at improving health-related quality of life balancing benefit and risk of treatment that often requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features (such as depression), fatigue, sleep disturbance and patient preferences and comorbidities; by shared decision-making with the patient. Initial management should focus on non-pharmacological therapies.	IV	D		100
Specific recommendations				
Non-pharmacological management				
Aerobic and strengthening exercise	Ia	A	Strong for	100
Cognitive behavioural therapies	Ia	A	Weak for	100
Multicomponent therapies	Ia	A	Weak for	93
Defined physical therapies: acupuncture or hydrotherapy	Ia	A	Weak for	93
Meditative movement therapies (qigong, yoga, tai chi) and mindfulness-based stress reduction	Ia	A	Weak for	71–73
Pharmacological management				
Amitriptyline (at low dose)	Ia	A	Weak for	100
Duloxetine or milnacipran	Ia	A	Weak for	100
Tramadol	Ib	A	Weak for	100
Pregabalin	Ia	A	Weak for	94
Cyclobenzaprine	Ia	A	Weak for	75

*Percentage of working group scoring at least 7 on 0–10 numerical rating scale assessing agreement.

therapy according to patient need, which may include pharmacological therapy.

Comparison with other recommendation

There are three recent guidelines on the management of FM from Canada, Israel and Germany that have been compared with respect to their recommendations.[105] These guidelines and our EULAR recommendations are in agreement on the principles of approach to management, the need for tailored therapy to the individual and the first-line role of non-pharmacological therapies. There are differences between our guidelines and previous guidelines, which can partly be explained by us using more recently available evidence. There are differences in the strength of recommendations relating to pharmacological therapies: anticonvulsants and SNRIs were strongly recommended by the Canadian and Israeli guidelines while the German and these EULAR guidelines provide a weak recommendation. There are also differences in relation to individual non-pharmacological therapies across guidelines in terms of whether they were assessed. For example, meditative movement is strongly recommended by the German guidelines, but recommended only for a minority of patients in Israel, while these EULAR guidelines provide a 'weak for' recommendation.

The committee recommended that an update is conducted after 5 years in order to determine whether for those therapies with relatively little current evidence further trials have been conducted and, second, whether any new therapies have emerged for the management of fibromyalgia.

Research priorities

In the course of discussion, we identified important questions in terms of guiding management where there was either insufficient (or often no) evidence base to guide decisions, that is, 'research gaps'. We discussed their relatively priority taking into account their potential to guide management, the likelihood that such studies could be conducted and were likely to be funded. We identified five such priority questions:

- Which type of exercise is most effective: strength and/or aerobic training?
- Are combined pharmacological and non-pharmacological approaches to management more effective than single-modality management?
- Are there characteristics of patients with fibromyalgia that predict response to specific therapies?
- How should fibromyalgia be managed when it occurs as a comorbidity to inflammatory arthritis?
- What aspects of a healthcare system optimise outcome for patients (who is best for the management of FM patients)?

Some of these questions are best answered by RCTs. Given, however, the expense of such studies and that they can take almost 10 years from identifying the questions to be answered to results being obtained, alternatives including registers and observational studies should be considered. These can be complemented by qualitative studies to determine the needs of patients.

Dissemination

These recommendations will be disseminated by the international working group through national rheumatology societies. This will include scientific meetings, newsletters and continuing education programmes. We will produce a summary of the recommendations suitable for dissemination through EULAR-affiliated patient groups and through national patient societies. We will investigate assessing agreement with the recommendations in the target population.

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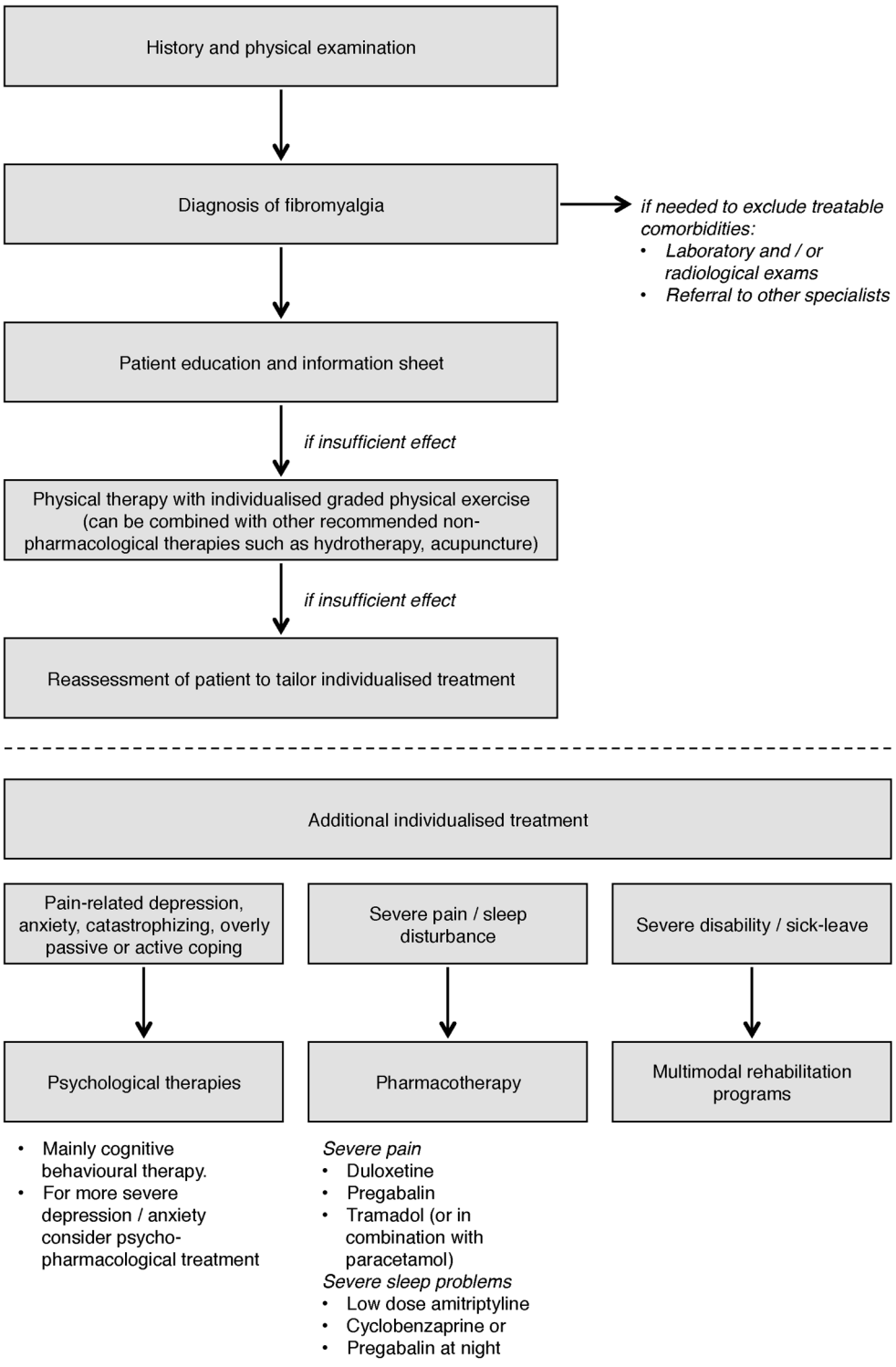
History and physical examination
Diagnosis of fibromyalgia
if needed to exclude treatable comorbidities:
• Laboratory and / or radiological exams
• Referral to other specialists
Patient education and information sheet
if insufficient effect
Physical therapy with individualised graded physical exercise (can be combined with other recommended non-pharmacological therapies such as hydrotherapy, acupuncture)
if insufficient effect
Reassessment of patient to tailor individualised treatment
Additional individualised treatment
Pain-related depression, anxiety, catastrophizing, overly passive or active coping
Severe pain / sleep disturbance
Severe disability / sick-leave
Psychological therapies
Pharmacotherapy
Multimodal rehabilitation programs
• Mainly cognitive behavioural therapy.
• For more severe depression / anxiety consider psycho-pharmacological treatment
Severe pain
• Duloxetine
• Pregabalin
• Tramadol (or in combination with paracetamol)
Severe sleep problems
• Low dose amitriptyline
• Cyclobenzaprine or
• Pregabalin at night

Figure 2 Management recommendations as flow chart.

SUMMARY

In summary, these revised EULAR recommendations newly incorporate a decade of evidence in relation to the pharmacological and non-pharmacological management of fibromyalgia. They allow EULAR to move from recommendations that are predominantly based on expert opinion to ones that are firmly based on scientific evidence from high-quality reviews and meta-analyses. Despite this evidence, however, the size of effect for many treatments is relatively modest. We propose focusing on the research priorities we outline to address issues clarifying to whom certain interventions may best be delivered, their effect in combination, matching patients to therapies and the organisation of healthcare systems to optimise outcome.

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Contributors GJM, FA, PS-P, EC and GTJ were applicants on the grant. EF and LED undertook the literature search and together with FA identified eligible reviews. EF, LED, FA and CK evaluated the quality of each of the eligible reviews. GTJ led the evaluation of non-pharmacological therapies and FA and CK led the evaluation of pharmacological therapies. GJM drafted the manuscript with input from GTJ, WH, EC, CK and EK. All authors (with the exception of FA and EF) participated in a 2-day project meeting, and all authors made important intellectual contributions to the manuscript.

Funding The project was funded by EULAR.

Competing interests CK undertook work in this project supported by a fellowship from the Swiss Society for Rheumatology. SP has received personal fees from Pierre Fabre, Pfizer, Eli Lilly and Jazz pharmaceutical (advisory boards and research activities). EC has received personal fees from Pfizer, Eli Lilly and Tonix (advisory boards and speaker fees). WH has received personal fees from MSD and Grünenthal (speaker fees), was head of the steering committee of the German guidelines on fibromyalgia and is a member of the medical board of the German Fibromyalgia Association. GJM has received personal fees from Pfizer (research activities). EK reports personal fees from Lundbeck, Orion and research funding from Eli Lilly. GMM reports personal fees from Pfizer, A Menarini, Hospiri and BMS, and has received research funding from AbbVie and Pfizer. PS-P reports personal fees from Abbott, Roche, Pfizer, UCB, MSD and has received research funding from Pfizer, UCB, Roche.

Provenance and peer review Not commissioned; externally peer reviewed.

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Ann Rheum Dis: first published as 10.1136/annrheumdis-2016-209724 on 4 July 2016. Downloaded from http://ard.bmj.com/ on February 3, 2023 by guest. Protected by copyright.

Arthritis Care & Research
Vol. 62, No. 5, May 2010, pp 600–610
DOI 10.1002/acr.20140
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ORIGINAL ARTICLE

The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors as Provisional. This signifies that the criteria set has been quantitatively validated using patient data, but it has not undergone validation based on an external data set. All ACR-approved criteria sets are expected to undergo intermittent updates.

As disclosed in the manuscript, these criteria were developed with support from the study sponsor, Lilly Research Laboratories. The study sponsor placed no restrictions, offered no input or guidance on the conduct of the study, did not participate in the design of the study, see the results of the study, or review the manuscript or submitted abstracts prior to the submission of the paper. The recipient of the grant was Arthritis Research Center Foundation, Inc. The authors received no compensation. The ACR found the criteria to be methodologically rigorous and clinically meaningful.

ACR is an independent professional, medical and scientific society which does not guarantee, warrant or endorse any commercial product or service. The ACR received no compensation for its approval of these criteria.

Objective. **To develop simple, practical criteria for clinical diagnosis of fibromyalgia that are suitable for use in primary and specialty care and that do not require a tender point examination, and to provide a severity scale for characteristic fibromyalgia symptoms.**

Methods. **We performed a multicenter study of 829 previously diagnosed fibromyalgia patients and controls using physician physical and interview examinations, including a widespread pain index (WPI), a measure of the number of painful body regions. Random forest and recursive partitioning analyses were used to guide the development of a case definition of fibromyalgia, to develop criteria, and to construct a symptom severity (SS) scale.**

Results. **Approximately 25% of fibromyalgia patients did not satisfy the American College of Rheumatology (ACR) 1990 classification criteria at the time of the study. The most important diagnostic variables were WPI and categorical scales for cognitive symptoms, unrefreshed sleep, fatigue, and number of somatic symptoms. The categorical scales were summed to create an SS scale. We combined the SS scale and the WPI to recommend a new case definition of fibromyalgia: (WPI ≥7 AND SS ≥5) OR (WPI 3–6 AND SS ≥9).**

Conclusion. **This simple clinical case definition of fibromyalgia correctly classifies 88.1% of cases classified by the ACR classification criteria, and does not require a physical or tender point examination. The SS scale enables assessment of fibromyalgia symptom severity in persons with current or previous fibromyalgia, and in those to whom the criteria have not been applied. It will be especially useful in the longitudinal evaluation of patients with marked symptom variability.**

INTRODUCTION

The introduction of the American College of Rheumatology (ACR) fibromyalgia classification criteria 20 years ago began an era of increased recognition of the syndrome (1). The criteria required tenderness on pressure (tender points) in at least 11 of 18 specified sites and the presence of widespread pain for diagnosis. Widespread pain was defined as axial pain, left- and right-sided pain, and upper and lower segment pain.

Over time, a series of objections to the ACR classification criteria developed, some practical and some philosophi-

Supported by Lilly Research Laboratories.

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cal. First, it became increasingly clear that the tender point count was rarely performed in primary care where most fibromyalgia diagnoses occurred, and when performed, was performed incorrectly (2). Many physicians did not know how to examine for tender points and some simply refused to do so (3). Consequently, fibromyalgia diagnosis in practice has often been a symptom-based diagnosis.

Second, the importance of symptoms that had not been considered by the ACR Multicenter Criteria Committee became increasingly known and appreciated as key fibromyalgia features: for example, fatigue, cognitive symptoms, and the extent of somatic symptoms (4–7). In addition, a number of fibromyalgia experts believed that tender points obscured important considerations and erroneously linked the disorder to peripheral muscle abnormality (8). Finally, some physicians considered that fibromyalgia was a spectrum disorder and was not well served by dichotomous criteria (9).

There was still another important problem with fibromyalgia diagnosis. Patients who improved or whose symptoms and tender points decreased could fail to satisfy the ACR 1990 classification definition. It was not clear how to categorize or assess these patients. In addition, the ACR classification criteria set such a high bar for diagnosis that there was little variation in symptoms among fibromyalgia patients. These two considerations suggested the need for a broad-based severity scale that could differentiate among patients according to the level of fibromyalgia symptoms.

With all of these considerations in mind, we conducted a multicenter study of patients with a diagnosis of fibromyalgia and a control group of rheumatic disease patients with noninflammatory disorders to address the issues of fibromyalgia diagnosis and symptom severity. The objectives of this study were: 1) to identify non–tender point diagnostic criteria for fibromyalgia; these criteria are not meant to replace the ACR classification criteria, but to represent an alternative method of diagnosis; 2) to integrate severity scale–based symptoms in these new clinical criteria, built on the characteristic features of fibromyalgia; these criteria should be suitable for use in primary care and helpful in following patients longitudinally; and 3) to develop a fibromyalgia symptom severity (SS) scale.

To accomplish these objectives, we employed a 2-stage design. In the first stage, we collected an extensive set of patient and physician variables from 514 patients and controls, including an index of pain extent (widespread pain index [WPI]) and characteristic fibromyalgia symptoms. From the resultant data, models were developed for the surrogate classification criteria, diagnostic criteria, and a severity scale. In the second stage, 315 additional patients and controls were assessed by physicians with a reduced set of variables in a physician questionnaire format that could be reduced to a single page suitable for primary care use. The purpose of the phase 2 study was to see if a shortened, practical physician questionnaire would work as well in categorizing fibromyalgia as the longer, more detailed phase 1 assessments. Thus, we primarily report phase 1 data except for comparisons of classification rates and severity variables. Survey criteria, based on patient self-report, will be the subject of a separate report.

Dr. Clauw has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Pfizer, Lilly, Forest, Cypress Biosciences, Pierre Fabre, UCB, and AstraZeneca. Dr. Fitzcharles has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Pfizer, Lilly, and Boehringer Ingelheim, and has given expert testimony for various medicolegal and law firms and received a fee. Dr. Goldenberg has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Forest, Pfizer, and Lilly. Dr. Anthony S. Russell has received consultant fees (less than $10,000 each) from Amgen/Wyeth, Schering-Plough, UCB, and Abbott Canada, and speaking fees (less than $10,000 each) from Roche and BMS. Dr. I. Jon Russell has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Johnson & Johnson and UCB, and (more than $10,000 each) from Pfizer, Lilly, and Jazz. Dr. Winfield has received consultant fees, speaking fees, and/or honoraria (more than $10,000 each) from Lilly, Pfizer, Forest, and Jazz, and has given expert testimony for medicolegal and various law firms and received a fee. Dr. Yunus has received speaking fees (more than $10,000) from Forest Laboratories.

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Submitted for publication August 24, 2009; accepted in revised form February 10, 2010.

SUBJECTS AND METHODS

Study subjects and physicians. We recruited study physicians by selecting randomly from a list of 113 rheumatologists who were members of the ACR and who indicated an interest in participating in the study after an e-mail solicitation. We also included 5 physicians with known fibromyalgia expertise selected from the authors (FW, DJC, MAF, DLG, ASK, PM, ASR, IJR, JBW).

Participating physicians had to be certain that they would see 10 fibromyalgia patients and 10 noninflammatory controls within a 4-month period. They had to be experienced with fibromyalgia patients and the fibromyalgia tender point examination. All of the physicians completed a short instructional questionnaire on the Internet and satisfactorily completed a brief examination on study requirements and methods. We required that the physician, not an assistant, complete physician assessment forms, and that patient forms could only be completed by the patient.

We required the fibromyalgia study patients to have a previous diagnosis of fibromyalgia. They were enrolled as they appeared in the clinic for usual care (not by being recalled) and without consideration of current diagnosis, severity, or other characteristics. Fibromyalgia subjects must have been diagnosed with fibromyalgia by the same examining rheumatologist prior to the date of study assessment. Patients diagnosed with fibromyalgia could have been diagnosed on clinical grounds or by the ACR classification criteria (10). It was not a requirement of diagnosis to have satisfied the ACR classification criteria. Of the 30 physicians contributing valid patients to phase 1 of the study, 6 used only clinical diagnosis, 9 used only the ACR classification criteria diagnosis, and 15 diagnosed some

patients using clinical methods and some patients using the ACR methods. Among the expert physicians, 4 used clinical diagnosis, 4 used the ACR classification criteria diagnosis, and 2 used both methods.

Control subjects were patients with noninflammatory painful disorders such as degenerative neck and back pain syndromes or regional disorders, osteoarthritis, tendonitis, or similar disorders who had not been diagnosed previously as having fibromyalgia and who were of the same sex and were no more than 10 years younger or 10 years older than the fibromyalgia case. As with the fibromyalgia patients, the control subjects must have had a prior control diagnosis. Patients with any inflammatory rheumatic disorder (e.g., rheumatoid arthritis), active cancer, fractures, defined neuropathic causes of pain, or other nonrheumatic causes for pain were excluded from the study.

In phase 1, we enrolled 610 patients from 32 referring physicians between December 2, 2008, and April 30, 2009. We excluded 96 patients (15.7%) for one or more protocol violations. Two physicians enrolled fewer than 10 patients, 1 and 5 patients each, and their patients were excluded because of insufficient site enrollments. We also excluded subjects for invalid control diagnoses (n = 12) and for failure to match fibromyalgia patients with controls of the same sex within 10 years of age by sex (n = 96) by the time of study closure. After exclusions, there were 514 subjects (mean 17 and median 20 per center). From the group of physician participants there were 10 "experts," defined as having published on fibromyalgia in the medical literature.

Study variables: phase 1. We instructed study sites to have patients complete their forms before seeing the physician. Physicians were instructed not to look at the patient forms. Physicians' staff was asked to check each patient's form for completeness and request completion of missing items before the patient left the clinic.

Patient variables: phase 1. Patients were asked to indicate in which of 19 body areas they had pain during the last week. These areas were those previously described as part of the Regional Pain Scale (renamed here as the WPI) (11). We also analyzed the WPI as a categorical variable, with categories 0, 1, 2, and 3 for values of 0, 1–3, 4–6, and ≥7 of the WPI, respectively. The categories were determined by study analyses (see below).

Patients completed 7 categorical scales for symptoms over the past week that were scored as: 0 = no problem; 1 = slight or mild problems, generally mild or intermittent; 2 = moderate, considerable problems, often present and/or at a moderate level; and 3 = severe, pervasive, continuous, life-disturbing problems. Symptoms were assessed using the following words: pain, fatigue, trouble with sleep, trouble with anxiety or depression, problems awaking unrefreshed, and overall severity of your arthritis or fibromyalgia problem. In addition, patients completed 4 visual analog scales that were scored as 0–10. The scale questions and anchors were 1) severity of pain over the last week, with anchors from no pain to severe pain; 2) how much of a problem has fatigue or tiredness been for you over the past week?, with anchors from fatigue is no problem to fatigue is a major problem; 3) how much of a problem has sleep (i.e., resting at night) been for you in the past week?, with anchors from sleep is no problem to sleep is a major problem; and 4) how much of a problem has waking up unrefreshed been for you in the last week?, with anchors from waking up unrefreshed is no problem to waking up unrefreshed is a major problem. Patients also completed the Health Assessment Questionnaire II functional disability scale (12). Patients indicated the number of medications they used in the last month to help control pain, and reported the extent of morning stiffness.

We also asked patients to indicate which of the following symptoms they experienced in the last 3 months: blurred vision or problems focusing; dry eyes; ringing in ears; hearing difficulties; mouth sores; dry mouth; loss of or change in taste; headache; dizziness; fever; chest pain; shortness of breath; wheezing (asthma); loss of appetite; nausea; heartburn; indigestion or belching; pain or discomfort in the upper abdomen (stomach); liver problems; pain or cramps in the lower abdomen (colon); diarrhea (frequent, explosive watery bowel movements, severe); constipation; black or tarry stools (not from iron); vomiting; joint pain; joint swelling; low back pain; muscle pain; neck pain; weakness of muscles; tiredness (fatigue); depression; insomnia; nervousness (anxiety); seizures or convulsions; trouble thinking or remembering; easy bruising; hives or welts; itching; rash; loss of hair; red, white, and blue skin color changes in fingers on exposure to cold or with emotional upset; sun sensitivity (unusual skin reaction, not sunburn); yellow skin or eyes (jaundice); fluid-filled blisters; numbness/tingling/burning; swelling of the hands, legs, feet, or ankles (not due to arthritis); irritable bowel syndrome; faintness; frequent urination; painful urination; pain, fullness, or discomfort in the bladder region; sensitivity to bright lights, loud noises, or odors; fatigue severe enough to limit daily activity; tender lymph nodes; or frequent sore throats. We summed the positive replies to create a 0–56 count of somatic symptoms scale.

Physician variables: phase 1. Physicians were asked not to look at the forms completed by the patient. Physicians indicated their certainty of the prior diagnosis on a 0–10 scale (0 = very uncertain, 10 = very certain). They performed the ACR tender point count (0–18) (1) and completed the same painful body region scale as their patients did. They completed categorical scales for pain, fatigue, sleep disturbance, cognitive symptoms, waking unrefreshed, and overall (global) severity using the same categorical scoring as the patients did. Physicians also indicated if the patients had the following symptoms: muscle pain, irritable bowel syndrome, fatigue, cognitive problems, muscle weakness, headache, pain/cramps in the abdomen, paresthesias, dizziness, sleep problem, depression, constipation, diarrhea, interstitial cystitis, anxiety, and muscle tenderness.

We then provided the physicians a list of symptoms for reference purposes and asked them to categorize the patients as having few or no somatic symptoms, a moderate number of symptoms, or a great deal of symptoms. The reference list consisted of: muscle pain, irritable bowel

syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

Based on the study results described below, we created an SS scale by summing the 0–3 scores of somatic symptoms, waking unrefreshed, cognition, and fatigue into a 0–12 scale.

Phase 2 study and variables. The methods and rules for physician and patient recruitment were the same for the second phase, except that the authors with known fibromyalgia expertise were not recruited. In addition, patients did not complete questionnaires. At the time of study closure, 315 valid patients had been enrolled. The phase 2 form was simplified and completed only by the physician. It contained the following items: a categorical WPI and a question about widespread pain. Physicians were provided with a list of the widespread pain regions (scored as 0–3, 4–6, 7–10, or ≥11), but could not score the individual regions. Physicians performed and recorded a tender point examination; indicated the presence or absence of muscle pain, muscle tenderness, and irritable bowel syndrome; and provided a rating of the extent of somatic symptoms (few or no symptoms, a moderate number of symptoms, or a great deal of symptoms). For reference, a list of 41 symptoms was supplied on the questionnaire. Finally, we included categorical scales for sleep disturbance, unrefreshed sleep, cognitive problems, and fatigue, with scoring as described above.

Statistical methods. On completion, study forms were faxed to the National Data Bank for Rheumatic Diseases, Wichita, Kansa, for processing. They were reviewed for missing data, and if such data were found, the examining physician was contacted immediately for corrections, if possible. Missing patient data and physician data that were not correctable within one week were left as missing. Missing data were rare: in phase 1, 81.7% of patients had no missing data, 12.8% had 1 missing data point, and 1.6% had 3–8 missing data points.

In phase 1 analyses, we considered 3 groups of classifier variables: a short set of variables, an intermediate set, and a complete set. The short set included the WPI and categorical scales for pain, fatigue, sleep disturbance, mood, cognitive problems, somatic symptoms, and unrefreshed sleep. The intermediate set included all of the variables in the short set plus all of the individual somatic symptoms. The complete set included all of the study variables. We anticipated that, because of the need for simplicity, the criteria and severity scales would probably come from the short set. We analyzed the intermediate set under the consideration that the individual symptoms might also be important. The complete set allowed us to compare the 3 sets as to their classifying value and to understand what might be lost in shortening the set of variables.

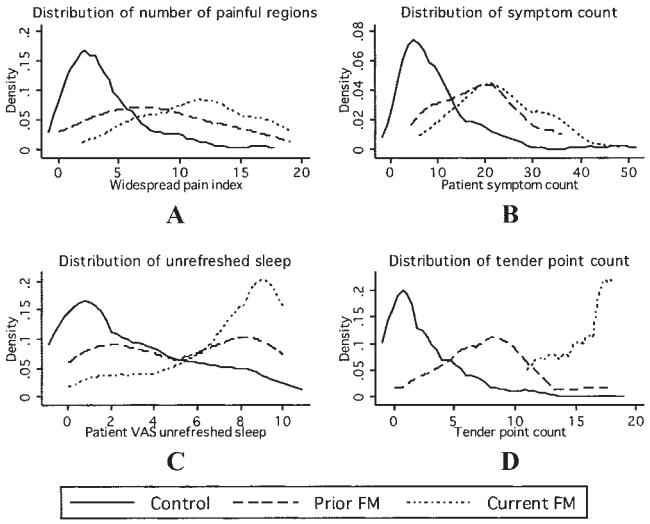

Figure 1. Distribution of key fibromyalgia (FM) variables in controls and patients with current or prior FM (phase 1). VAS = visual analog scale.

Comparisons between groups used *t*-tests, regression analyses with dummy variables, and chi-square tests, as indicated. Spearman's coefficients were used for correlation analyses. Data were analyzed using Stata, version 10.1 (StataCorp), and the R statistical package, version 2.81. Random forest analysis was used to determine variable importance and "out-of-bag" error rates (10,11) using the R statistical package. The out-of-bag error rate is a robust measure of misclassification error. Variable importance is described by the mean decrease in accuracy criterion or the Gini Index, and it represents a ranking of variables in terms of their importance as predictors. The mean decrease in accuracy is thought to be a better measure: ". . . the Gini Index reflects the overall goodness of fit, while the predictive accuracy depends on how well the model actually predicts. The two are related, but they measure different things. Breiman argues that the decrease in predictive accuracy is the more direct, stable and meaningful indicator of variable importance (personal communication)" (13). Classification tree analysis used the rpart recursive partitioning R analysis programs to determine preliminary cut points for criteria variables (14). Figure 1 describes the distribution of study variables using a probability density function. The reader can think of the probability density function as a "smoothed-out" version of a histogram.

Conflict of interest and ethics. Examining physicians were each compensated $2,000 for their work in interviewing, examining, and completing study forms for 10 patients and 10 controls. The study authors received no compensation. The study was approved by the Via Christi Institutional Review Board.

RESULTS

Demographics. Physicians enrolled 258 valid patients in phase 1 whose clinical diagnosis was fibromyalgia and

Table 1. Selected clinical characteristics of patients with current or prior fibromyalgia and controls in phase 1*

Variable	Current fibromyalgia	Prior fibromyalgia	Controls
No. of patients (%)	196 (38.1)	67 (13.0)	251 (48.1)
Widespread pain index (0–19)	11.4 ± 4.4	8.2 ± 5.0	3.8 ± 3.2
Physician widespread pain index (0–19)	11.4 ± 4.1	7.2 ± 3.9	3.3 ± 2.5
Widespread pain, % patients	92.9	56.7	31.1
Widespread pain, % physicians	93.9	59.7	24.3
Tender point count (0–18)	15.9 ± 2.3	7.9 ± 4.1	2.5 ± 3.0
ACR 1990 classification criteria positive, % patients	92.9	0.0	0.0
ACR 1990 classification criteria positive, % physicians	93.9	0.0	0.0
ACR 1990 classification criteria positive, % patients or physicians	100.0	0.0	0.0
Physician global severity, categorical (0–3)	2.1	1.5	1.1
Patient global severity, categorical (0–3)	2.4	1.8	1.4
Patient symptom count (0–48)	22.9 ± 8.8	18.2 ± 8.4	9.7 ± 8.4
Physician somatic symptoms (0–3)	2.3 ± 0.7	1.9 ± 0.7	1.2 ± 0.5
HAQ-II score (0–3)	1.3 ± 0.6	1.0 ± 0.7	0.7 ± 0.6
Patient VAS unrefreshed sleep (0–10)	7.3 ± 2.7	5.2 ± 3.4	3.1 ± 3.0
Patient VAS sleep (0–10)	6.5 ± 2.8	4.4 ± 3.2	3.3 ± 3.0
Patient VAS pain (0–10)	6.5 ± 2.3	4.9 ± 2.7	4.1 ± 2.8
Patient VAS fatigue (0–10)	7.0 ± 2.4	5.0 ± 3.1	3.3 ± 2.9
Symptom severity scale (0–12)†	8.0 ± 2.6	6.0 ± 2.6	3.3 ± 2.2
No. of pain medications	3.3 ± 2.3	2.5 ± 1.4	1.9 ± 1.9

* Values are the mean ± SD unless otherwise indicated. ACR = American College of Rheumatology; HAQ-II = Health Assessment Questionnaire II; VAS = visual analog scale.
† Sum of physician somatic symptoms, physician waking unrefreshed, physician cognition, and physician fatigue.

256 who were control subjects. Fibromyalgia subjects were slightly older than controls (mean ± SD age 54.6 ± 12.9 versus 52.3 ± 12.2 years; $P = 0.035$), but did not differ by the percentage of males (8.2% versus 9.0%; $P = 0.732$), percentage of non-Hispanic whites (86.8% versus 85.9%; $P = 0.770$), or education level (mean ± SD 14.2 ± 2.1 versus 14.3 ± 2.2 years; $P = 0.517$).

Diagnosis and diagnostic methods. ACR classification criteria were used in 63.6% of fibromyalgia diagnoses and clinical diagnosis was used in 36.4% of fibromyalgia diagnoses. At the time of the study examination, 74.5% of patients who had been previously diagnosed with fibromyalgia satisfied the ACR classification criteria and 2.0% of controls satisfied the ACR classification criteria. Based on these data, we categorized patients into 3 groups based on prior diagnosis and ACR classification criteria status: 196 patients (38.1%) with current fibromyalgia (ACR classification criteria positive, physician fibromyalgia diagnosis positive), 67 patients (13.0%) with prior fibromyalgia (ACR classification criteria negative, physician fibromyalgia diagnosis positive), and 251 patients (48.1%) who were neither current nor prior fibromyalgia patients (control subjects) (Table 1). Using a 0–10 physician certainty of prior diagnosis scale, the mean certainties were: fibromyalgia 9.4, prior fibromyalgia 8.7, and control diagnosis 9.1. Patients previously diagnosed by clinical criteria were more likely to be classified as prior fibromyalgia (38.3%) compared with patients previously diagnosed by the ACR classification criteria (18.9%; $P < 0.001$). The proportion of patients who were controls or had prior or current fibromyalgia did not differ between the group of 10 expert physicians and the 20 clinical rheumatologists ($P = 0.640$).

Characteristics of patients by fibromyalgia status. There was a clear difference in clinical findings and symptom severity among the groups, the current fibromyalgia patients having the greatest symptom severity with prior fibromyalgia generally occupying the severity scale midpoint between current fibromyalgia and controls (Table 1). However, for the count of patient-endorsed somatic symptoms, the physician somatic symptom scale, and the SS scale, prior fibromyalgia patients had scores that were somewhat closer to current fibromyalgia patients than to control subjects. Figure 1 shows differences between groups for key variables. The tender point count (Figure 1D) demonstrates the clearest distinction between groups, followed by unrefreshed sleep (Figure 1C). Prior and current fibromyalgia patients had similar distributions of somatic symptom counts (Figure 1B), while prior fibromyalgia had the WPI shifted somewhat to the left (Figure 1A). Taken as a whole, these data show that approximately 25% of patients considered to have fibromyalgia by their physicians do not satisfy ACR classification criteria for fibromyalgia, and that they appear to have an intermediate severity position between fibromyalgia patients and control subjects, except for somatic symptoms.

Misclassification rates and fibromyalgia classifiers. To determine variables that best identify fibromyalgia and to examine the predictive power of study variables without the use of tender points, we divided the subjects into ACR

Table 2. Random forest out-of-bag misclassification rates for physician and patient variable groups in the diagnosis of ACR 1990 classification criteria–positive fibromyalgia (phase 1)*

Variable group	Error rate (continuous WPI)	Error rate (categorical WPI)	Error rate (no WPI, no muscle variables)	Error rate (no WPI, no muscle tenderness)	Error rate (no WPI)
Physician evaluator, %					
Complete	6.2	6.4	NA	NA	NA
Intermediate	6.4	7.3	16.1	14.0	10.3
Short	8.9	10.3	18.4	NA	NA
Patient evaluator, %					
Complete	12.7	NA			
Intermediate	14.1	NA			
Short	13.9	NA			

* Prior fibromyalgia cases are excluded from the analysis. ACR = American College of Rheumatology; WPI = widespread pain index; complete group = all study variables; NA = not applicable; intermediate group = short group variables plus all individual somatic symptoms; short group = WPI and categorical scales for pain, fatigue, sleep disturbance, mood, cognitive problems, somatic symptoms, and unrefreshed sleep.

classification criteria–positive (all patients satisfying the ACR classification criteria) and ACR classification criteria–negative cases (all controls satisfying the ACR criteria), after excluding patients who physicians designated as having fibromyalgia but who did not satisfy the ACR classification criteria. We then used random forest analyses to rank physician predictors of fibromyalgia by their importance and to obtain misclassification rates. We examined the WPI as a continuous variable (0–19) and also after splitting it into categories at 0, 1–3, 4–6, and ≥7. In these analyses, we examined the complete set of variables, an intermediate set, and a short set (Table 2).

Depending on the number of variables in the model (variable group) and whether the WPI was used as a continuous or a categorical variable, physician study variables misclassified fibromyalgia cases and controls at rates of 6.2–10.3% (Table 2). Figure 2A shows that the WPI and muscle tenderness were the most important variables in the classification of cases and noncases. These data provide an estimate of the lowest misclassification rates of surrogate criteria obtainable under optimum data mining conditions.

We next performed analyses to determine misclassification rates when muscle variables (muscle pain, muscle tenderness) and the WPI were removed from the models. Removing all of the muscle variables and the WPI resulted in a misclassification rate of 16.1% (Table 2). Using the same intermediate model but keeping muscle pain reduced the error rate to 14.0%, whereas removing the WPI but leaving all muscle pain and muscle tenderness variables resulted in a misclassification rate of 10.3%. Using the short variable list (that never contains muscle pain or muscle weakness), the misclassification rate was 18.4%. These data show that misclassification rates obtainable under optimum data mining conditions that do not contain ACR classification criteria–related variables are between 16.1% and 18.4% (14.0% if muscle pain is allowed).

Based on the information in Table 2, we selected the variables contained in the intermediate WPI categorical model (7.3% error rate) for further study because that model represented the best practical model that contained the WPI and muscle data (Table 2) and had the lowest misclassification rate. Random forest analysis provides information on variable importance and misclassification rates, but does not provide information about the optimum cut points for study variables. We then applied recursive partitioning to the data and determined that values of the WPI ≥7 best identified fibromyalgia cases and values ≤6 best identified control cases according to their ACR classification criteria status.

In addition, in the comparison of ACR classification criteria–positive versus ACR classification criteria–negative cases (excluding prior fibromyalgia), the correct classification rates for phase 1 ran between 89.0% and 92.6%, with higher rates being obtained in phase 2 analyses. When all of the patients were considered, WPI ≥7 performed about as well (83.6%) as physician diagnosis (84.1%) in the classification of fibromyalgia in phase 1, again with improvement in the phase 2 data. There was some gain obtained by including information about muscle pain or muscle tenderness. Overall, these data show that patients who satisfy the ACR classification criteria can be identified with an acceptable rate of error by the use of the WPI alone, and with very slightly better results if muscle tenderness or muscle pain is assessed.

The SS scale and fibromyalgia diagnostic criteria. To build and identify an alternative definition of fibromyalgia and to create an SS scale, we turned back to the intermediate categorical model that excluded the WPI and muscle variables (Table 2 and Figure 2B). From Figure 2B, we identified 6 categorical rating scale variables that had high importance levels (somatic symptoms, waking unrefreshed, cognition, fatigue, sleep problems, and mood). As shown in Table 3, these variables are strongly correlated with the tender point count and the WPI. For comparison, pain intensity, with correlation coefficients of 0.346 and 0.437, respectively, was less strongly correlated. We created an SS scale by summing the 0–3 scores of somatic symptoms, waking unrefreshed, cognition, and fatigue, into a 0–12 scale.

When applied to study patients, using the ACR classifi-

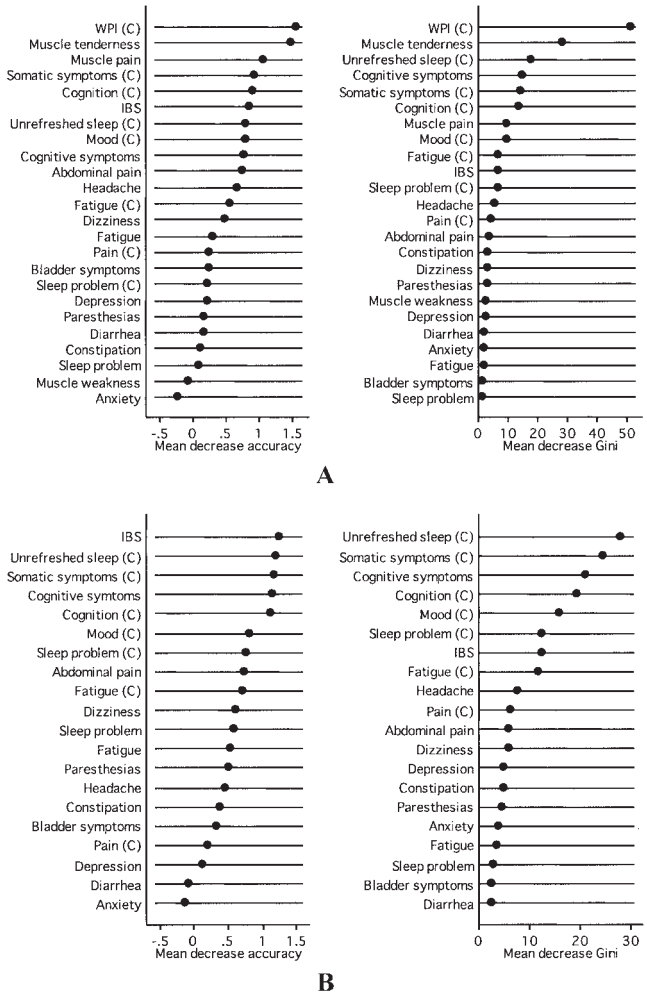

Figure 2. **A**, Variable importance (physician variables) in distinguishing fibromyalgia from controls in intermediate detail physician evaluation by random forest analysis in phase 1, including the widespread pain index (WPI) and muscle symptoms. **B**, Variable importance (physician variables) in distinguishing fibromyalgia from controls in intermediate detail physician evaluation in phase 1 by random forest analysis, excluding the Regional Pain Scale (WPI) and muscle symptoms. Other variables are present/absent conditions. Variable importance is described by the mean decrease in accuracy criterion or the Gini Index, and it represents a ranking of variables in terms of their importance as predictors. The Gini Index reflects the overall goodness of fit, while the predictive accuracy depends on how well the model actually predicts. The two are related, but they measure different things (13). The mean decrease in accuracy is thought to be a better measure. C = categorical scale; IBS = irritable bowel syndrome.

cation criteria definition of fibromyalgia, the mean ± SD SS scale score for fibromyalgia was 8.0 ± 2.6, for prior fibromyalgia was 6.0 ± 2.6, and for controls was 3.3 ± 2.2 (Table 1). The SS scale was strongly correlated with the WPI (0.733) and the tender point count (0.680), and was the strongest correlate of WPI after the tender point count, which was correlated with the WPI at 0.773 (Table 3). As shown in Figure 3, the SS scale appropriately follows the definitions of ACR classification criteria–positive fibromyalgia, prior fibromyalgia, and non-fibromyalgia, suggesting that it can categorize fibromyalgia symptom severity.

Table 3. Spearman's correlation coefficients for all study subjects (phase 1)

Variable	Tender point count	Widespread pain index
Tender point count	1.000	0.773
Widespread pain index	0.773	1.000
Symptom severity scale	0.680	0.733
Symptom severity scale*	0.672	0.713
Somatic symptoms†	0.631	0.683
Waking unrefreshed†	0.622	0.656
Cognition†	0.575	0.592
Fatigue†	0.548	0.604
Sleep problems	0.524	0.546
Mood	0.504	0.534
Pain	0.346	0.437

* Five-component symptom severity scale (includes mood).
† Component of 4-component symptom severity scale.

Fibromyalgia case definition: diagnostic criteria. We used the SS scale and the WPI to recommend a new case definition of fibromyalgia: (WPI ≥7 AND SS ≥5) OR (WPI 3–6 AND SS ≥9) (Table 4). This definition recognizes that fibromyalgia is more than just a high WPI scale by requiring an SS scale score ≥5, and recognizes that a high level (SS ≥9) of symptoms should be sufficient for diagnosis, provided that there is sufficient body pain. Using this definition, 9.1% of controls would be diagnosed as having fibromyalgia, 53.1% of prior fibromyalgia patients would be diagnosed as having fibromyalgia, and 14.1% of ACR classification criteria–positive cases would not be diagnosed as having fibromyalgia. Overall, the fibromyalgia rate among all of the study subjects would increase from 38.1% to 45.5% using the recommended definition. As shown in Table 5, using the ACR classification criteria as the gold standard, the diagnostic criteria diagnose 82.6% of cases correctly compared with the clinician's correct diagnosis rate of 84.1%.

We also used the SS scale to aid in the diagnosis of

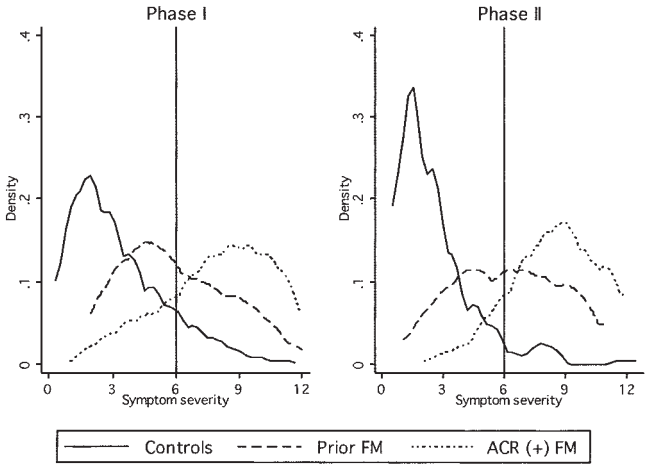

Figure 3. Distribution of severity scores using the American College of Rheumatology (ACR) 1990 classification criteria definition of fibromyalgia (FM) by category of FM diagnosis in phases 1 and 2. A symptom severity scale score >6 identifies patients satisfying the new diagnostic criteria in 92.3% of cases.

Table 4. Fibromyalgia diagnostic criteria

Criteria

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

1) Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥9.
2) Symptoms have been present at a similar level for at least 3 months.
3) The patient does not have a disorder that would otherwise explain the pain.

Ascertainment

1) WPI: note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.

Shoulder girdle, left	Hip (buttock, trochanter), left	Jaw, left	Upper back
Shoulder girdle, right	Hip (buttock, trochanter), right	Jaw, right	Lower back
Upper arm, left	Upper leg, left	Chest	Neck
Upper arm, right	Upper leg, right	Abdomen	
Lower arm, left	Lower leg, left		
Lower arm, right	Lower leg, right		

2) SS scale score:

Fatigue
Waking unrefreshed
Cognitive symptoms

For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:

0 = no problem
1 = slight or mild problems, generally mild or intermittent
2 = moderate, considerable problems, often present and/or at a moderate level
3 = severe: pervasive, continuous, life-disturbing problems

Considering somatic symptoms in general, indicate whether the patient has:*

0 = no symptoms
1 = few symptoms
2 = a moderate number of symptoms
3 = a great deal of symptoms

The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

* Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

clinical fibromyalgia, because Figure 3 suggests that severity scale criteria might be applicable. A severity score ≥7 correctly classifies 92.3% of cases identified by the new diagnostic criteria definition: (WPI ≥7 AND SS ≥5) OR (WPI 3–6 AND SS ≥9). When applied to the ACR classification criteria, correct classification falls to 79.2%. This

Table 5. Percentage of patients correctly classified according to ACR 1990 classification criteria status and diagnostic criteria*

Comparison	Phase 1		Phase 2	
	Prior FM excluded	All patients	Prior FM excluded	All patients
ACR classification criteria positive, FM patients		74.0		75.6
Classifying patients according to ACR 1990 classification criteria status				
ACR 1990 criteria vs. physician diagnosis		84.1		
ACR 1990 criteria vs. WPI ≥7	89.0	83.6	92.3	87.9
ACR 1990 criteria vs. WPI ≥7 plus muscle pain	89.9	84.6	95.2	90.5
ACR 1990 criteria vs. WPI ≥7 plus muscle tenderness	92.6	87.4	95.2	90.5
FM diagnostic criteria				
ACR 1990 classification criteria vs. diagnostic criteria ((WPI ≥7 AND SS ≥5) OR SS ≥9)	88.1	82.6	95.2	90.8
ACR 1990 classification criteria vs. categorical SS scale (SS ≥7)	84.3	79.2	88.8	84.5
Diagnostic criteria ((WPI ≥7 AND SS ≥5) OR SS ≥9) vs. categorical SS scale (SS ≥7)		92.3		89.2

* ACR = American College of Rheumatology; FM = fibromyalgia; WPI = widespread pain index; SS = symptom severity.

falloff is to be expected, as the definition of fibromyalgia is shifted in the new criteria definition. Using the newly proposed categorical definition for fibromyalgia, the mean ± SD SS scale score for fibromyalgia was 8.5 ± 2.0, and for non-fibromyalgia was 2.9 ± 1.6. Using the SS scale score cutoff of ≥7, the mean ± SD respective scores were 8.6 ± 1.8 and 2.8 ± 1.4.

Phase 2 validation. The ACR classification criteria were used in 74.6% of fibromyalgia diagnoses. Among patients diagnosed as having fibromyalgia, 76.0% met ACR classification criteria compared with 74.5% in the first phase of the study. We categorized the 315 patients into 3 groups based on prior diagnosis and current ACR classification criteria status: 42.2% with current fibromyalgia, 13.3% with prior fibromyalgia, and 44.4% who were neither current nor prior fibromyalgia patients. The validation sample was slightly different in the 2 phases (Figure 3), and criteria to identify ACR classification criteria cases worked slightly better in phase 2.

DISCUSSION

We are aware of the inherent problems in the diagnosis of somatic syndromes that lack objective physical or laboratory features or well-characterized pathologic findings. The utility of such diagnostic criteria is very dependent on the clinical setting. The initial ACR fibromyalgia classification criteria stipulated that chronic widespread pain was present for 3 months and it was understood that no other disease was thought by the examiner to be accounting for the chronic widespread pain. These ACR classification criteria performed well in specialty clinics and were very useful in providing some patient homogeneity for clinical trials. However, they have not been widely embraced in primary care.

The diagnostic criteria suggested here (Table 4) are not meant to replace the ACR classification criteria. Instead, they were designed to address certain realities. First, the clinical diagnosis in primary care does not ordinarily involve a tender point count or an adequately executed tender count when performed. Second, the case definition of fibromyalgia has changed somewhat with increasing recognition of the importance of cognitive problems and somatic symptoms, factors that were not even considered in the 1990 ACR classification criteria.

In developing new diagnostic criteria, we identified 2 variables that best defined fibromyalgia and its symptom spectrum: the WPI and the composite SS scale. The WPI, which strongly correlated with the tender point count and the SS scale, best identified patients diagnosed with the ACR classification criteria. We also selected the SS scale, a composite variable composed of physician-rated cognitive problems, unrefreshed sleep, fatigue, and somatic symptom count to measure fibromyalgia symptom severity. We used the WPI and the SS scale together to define fibromyalgia diagnostic criteria: (WPI ≥7 AND SS ≥5) OR (WPI 3–6 AND SS ≥9). We also used the SS scale alone to provide a measure of fibromyalgia symptom severity. In many respects, these criteria are similar in concept to those proposed by Yunus et al in 1981 (15). These authors allowed fewer tender points in the presence of many symptoms, and they stressed the importance of symptoms.

One of the important findings of the current study was that approximately 25% of diagnosed fibromyalgia patients in both phases of the study did not satisfy the ACR classification criteria, although they were considered to have fibromyalgia by their physicians. Neither the ACR classification criteria nor the diagnostic criteria suggested here provide a solution for this classification dilemma. It arises because fibromyalgia diagnosis is based on severity assessments. The loss of a tender point or a painful region for any reason, including improvement, can result in failing to meet classification or diagnostic criteria. Practically, the conundrum involves patients who have fibromyalgia but who do not meet criteria versus patients who do not have fibromyalgia because they do not meet criteria. In this respect, fibromyalgia differs from rheumatoid arthritis or systemic lupus erythematosus, illnesses that do not involve diagnosis based on symptom severity, where patients continue to have their condition even though they may subsequently not meet diagnostic criteria.

We suggest the use of the SS scale to quantify fibromyalgia symptom severity as a workable solution to this problem. As shown in Figure 3, the distribution of SS scale scores defines the 3 diagnostic categories and provides measurement of fibromyalgia symptom severity to patients who do and do not currently satisfy ACR fibromyalgia criteria. Practically, patients who have satisfied the ACR classification or diagnostic criteria at one time can be followed with the symptom scale, thereby linking current status to previous diagnosis.

In creating the SS scale we chose not to use the mood variable, although it had importance in Figures 2A and B. We chose not to include mood because we judged mood difficult to assess and because it might be a resultant feature rather than a primary feature of the illness. Although we omitted mood, it was correlated with the SS scale at 0.725 and with the components of the SS scale as follows: cognition 0.625, somatic symptoms 0.621, waking unrefreshed 0.619, and fatigue 0.612. In addition, as shown in Table 3, a 5-component SS scale that included mood did not perform as well as a 4-component scale. Unrefreshed sleep was a better measure than sleep disturbance and we recommend its use in the SS scale. However, in sensitivity analyses, it provided marginally better differentiating power; we suggest that either scale can be used, although unrefreshed sleep is better. Of the binary variables, irritable bowel syndrome, abdominal pain, and headache had variable importance. However, they added no power to correct classification and we did not include them in the diagnostic criteria.

In addition, in developing criteria for clinical diagnosis we were cognizant of the need to make the diagnostic criteria simple enough and easy enough so that they would actually be used in clinical practice. To that end, we used simple categorical scales for the symptom scale and compressed the WPI to a similar categorical scale. None of this guarantees that the scales will be used appropriately, but it is easy enough to use them appropriately, and the knowl-

edge that these are key factors will increase recognition of such important symptoms.

In designing this study, we were concerned that a simple questionnaire would lose too much information. Therefore, we used a complex series of questions and evaluation in phase 1. Based on the results in Table 2, which showed little gain from the complete data sets, we collapsed the questionnaire to categorical scales and changed the format to a form that could be used in the clinic. Results from phase 2 in Table 5 suggest that the criteria would work satisfactorily in the final format, which is included in Table 4.

Readers might wonder: why is it so difficult to make new fibromyalgia criteria? The central problem in fibromyalgia criteria is the absence of a gold standard or case definition. The ACR classification criteria, rightly criticized for circularity (16), created a de facto case definition by imposing the 11 tender point rules on top of a crude definition of widespread pain (17). Subsequent studies as well as the data of this study showed the importance of (improved) quantitative measures of body pain (18–22), and of the key variables that comprise the SS scale in characterizing fibromyalgia. The shift in the conceptualization of fibromyalgia that occurred in the clinic and in research studies, however, provided no clear case definition. In the current study, we derived an empirical case definition from the variable importance analyses. The diagnostic criteria and SS scale we have proposed shift the fibromyalgia definition somewhat toward important symptoms: first, the criteria can be satisfied by a high level of symptoms if the WPI score is not high enough; second, fibromyalgia symptoms are accorded appropriate importance by the provision of the SS scale.

The suggested diagnostic criteria create a small discordance between the older ACR classification criteria case definition and the current definition that we have proposed. However, it is clear that the ACR classification criteria are unable to provide a useful classification for the 25% of fibromyalgia cases we identified as prior fibromyalgia, something that can be somewhat ameliorated through the use of the SS scale. In addition, it should be remembered that physician diagnosis only correctly classified 84.1% of cases, while the proposed diagnostic criteria, even with shift of definition, identified 82.6% of patients correctly (Table 5).

We envision the use of the diagnostic criteria in the following ways: following a diagnosis of fibromyalgia by ACR classification or diagnostic criteria, the results of the SS scale can document baseline symptom severity. Should the patient subsequently not satisfy ACR classification or diagnostic criteria, the SS scale can be used to measure current symptom severity status and change in status without the contradiction of having a diagnosis of fibromyalgia but not satisfying fibromyalgia criteria at the same time. Of course, the SS scale can also be used at any time regardless of diagnostic status. The SS scale alone provides some diagnostic information, but does not include the WPI. It provides information as to symptom severity and it allows fibromyalgia to be seen as part of a continuum, as some have suggested. The criteria and severity scale also provide room for those who are uncomfortable with the fibromyalgia concept, as they can simply report the WPI and the SS scale.

Physicians who are used to the ACR classification criteria may be uncomfortable with the absence of a physical examination criterion in the new diagnostic criteria. However, 98.7% of the patients in the study satisfying the diagnostic criteria had a least 1 tender point and 96.3% had 3 or more tender points. Even though the new criteria do not include a physical examination criterion, all of the patients being diagnosed should have a physical examination, which may include examination of tender point sites. We would like to point out that implicit in the 1990 ACR classification criteria was the requirement that clinical examination and clinical judgment had excluded other causes of chronic widespread pain, and such an exclusion is also implicit in the proposed diagnostic criteria. It is important for physicians to perform an appropriate clinical assessment to exclude other diagnoses, and/or to identify potential coexisting rheumatic diseases that may require treatment themselves.

Although not a study requirement for enrollment, all of the patients with fibromyalgia diagnosed by physicians had symptoms for at least 3 months. However, the timeframe for the physician assessment of WPI and the SS scale was 1 week. We used this timeframe to more accurately determine the level of symptoms. The new diagnostic criteria require that patients diagnosed as having fibromyalgia will have had a similar level of symptoms for at least 3 months, in agreement with the ACR classification criteria.

Although we collected data directly from patients as well as data from physicians, patient data did not work as well in correct classification as physician data (Table 2). The best misclassification rate obtainable with patient data was 12.7% compared with 6.2% with physician data. This difference is related to the fact that it is the physician and not the patient who makes the diagnosis.

This study has a number of limitations. Although our goal was to develop simple, practical criteria for clinical diagnosis of fibromyalgia that are suitable for use in primary and specialty care, we did not study the performance of these criteria in primary care. We recommend that a followup study in the primary care setting be accomplished. We also did not test the criteria among those with other rheumatic conditions, and we recommend that this be done in the future, too. The patient population should include those with relevant differential diagnoses (i.e., other rheumatic conditions) to determine the rate of misclassification that may occur. If, as we expect, the diagnostic criteria perform well, it seems possible that the ACR classification criteria might be withdrawn.

In summary, we have developed a case definition and diagnostic criteria for fibromyalgia: (WPI $\geq$7 AND SS $\geq$5) OR (WPI 3–6 AND SS $\geq$9). This simple clinical case definition of fibromyalgia correctly classifies 88.1% of cases classified by the ACR classification criteria, and does not require a physical or tender point examination. The SS scale enables assessment of fibromyalgia symptom severity in persons with current or previous fibromyalgia, and in those to whom the criteria have not been applied. It will be especially useful in the longitudinal evaluation of patients with marked symptom variability.

ACKNOWLEDGMENTS

The authors thank Kimberly Harp of the National Data Bank for Rheumatic Diseases for her superb work with study physicians and their questionnaire submissions that insured study quality. The following physicians participated in the study by enrolling patients and performing evaluations: Micha Abeles, MD, Fu Flora Bai, MD, Jane H. Box, MD, Robert G. Carpenter, MD, Kimberly Carter Cerveny, MD, John J. Condemi, MD, Kathryn H. Dao, MD, Kathleen P. Flint, MD, Neil J. Gonter, MD, Sivalingam Kanagasegar, MD, Wendy W. Lee, MD, Robert W. Levin, MD, Michael W. Lindamood, MD, MPH, Ndudi Oparaeche, MD, Elizabeth Reinitz, MD, Russell R. Rothenberg, MD, Amjad Roumany, MD, Stuart L. Silverman, MD, FACP, FACR, Ekaterina V. Soforo, MD, Terence W. Starz, MD, Roland Staud, MD, Nicholas R. Straniero, Jr., MD, David H. Trock, MD, Sudhakar Tumuluri, MD, Peter D. Utsinger, MD, Corey W. Walker, MD, John B. Winfield, MD, Ibrahim S. Alghafeer, MD, Jeff A. Alloway, MD, Philip A. Baer, MD, FRCPC, Lan X. Chen, MD, PhD, Ara H. Dikranian, MD, Steven J. Golombek, MD, Andrew M. Jasek, MD, Alan J. Kivitz, MD, CPI, Sri L. Koneru, MD, Theresa A. Lawrence-Ford, MD, Frances Y. Leung, MD, FRCPC, Robert J. Meador, Jr., MD, Sherif A. Nasef, MD, Rakesh C. Patel, DO, Lynne S. Peterson, MD, Karina D. Torralba, MD, Anthony M. Turkiewicz, MD, Brian T. Walitt, MD, MPH, William S. Wilke, MD, and Karen E. Zagar, MD.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Wolfe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Wolfe, Clauw, Fitzcharles, Goldenberg, Katz, Anthony S. Russell, I. Jon Russell, Winfield, Yunus.

Acquisition of data. Wolfe, Clauw, Fitzcharles, Goldenberg, Katz, Mease, Anthony S. Russell.

Analysis and interpretation of data. Wolfe, Clauw, Goldenberg, Mease, Anthony S. Russell, I. Jon Russell, Winfield, Yunus.

ROLE OF THE STUDY SPONSOR

Lilly Research Laboratories did not participate in the design of the study, see the results of the study, or review the manuscript or submitted abstracts.

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RHEUMATOLOGY

Rheumatology 2022;61:3907–3911
https://doi.org/10.1093/rheumatology/keac340
Advance access publication 1 July 2022

BSR Guidelines

British Society for Rheumatology

Management of foot health in people with inflammatory arthritis: British Society for Rheumatology guideline scope

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Management of foot health in people with inflammatory arthritis: British Society for Rheumatology guideline scope

The guideline will be developed using the methods and processes outlined in Creating Clinical Guidelines: Our Protocol [1]. This development process to produce guidance, advice and recommendations for practice has National Institute for Health and Care Excellence (NICE) accreditation.

1 Why the guideline is needed

Foot problems are highly prevalent in adults, children and young people with inflammatory arthritis (IA), but their burden is often underestimated by health professionals. People with IA are often frustrated that concerns relating to their feet are ignored [2–4]. There are existing guidelines for foot health that may be applicable to IA. A regional podiatry group has developed management guidelines to support non-specialist podiatrists in the management of people with RA and related foot problems [5]. However, these guidelines are now nine years old and, while they are practitioner-facing, they relate only to RA instead of the wider spectrum of IA, do not include children and young people, and are not sensitive to the foot health needs of people from different cultural and religious backgrounds (e.g. footwear and orthotic device appearance and preferences for different materials). There are also standards embedded in the NICE guideline for RA highlighting the need to treat foot pathology [6]. These standards have an underpinning philosophy that encourages empowered self-care, patient involvement in service design, tailoring of services to patients' needs, promotion of informed choice, and

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NICE has accredited the process used by BSR to create its clinical guidelines. The term began on 27 February 2012 and the current renewed accreditation is valid until 28 January 2023. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

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Submitted 2 March 2022; accepted 6 June 2022

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timely and appropriate access to services where needed. However, they do not make recommendations about specific aspects of clinical management, such as particular foot problems and different rheumatic diseases. Furthermore, there is limited guidance as to when foot health experts should be consulted and there are no recommendations on which assessments or interventions should be performed. Finally, the Arthritis and Musculoskeletal Alliance (ARMA) have previously produced generic patient-facing Standards of Care for people with musculoskeletal foot health problems [7] and children and young people with JIA [8]. These outlined what patients should expect from services at that time, and the latter recognize the need for specialist podiatry reviews for people with JIA. Despite this, neither provide clinicians with guidance for treatment and both standards are now over a decade old. A survey of non-specialist podiatrists in the UK found that over 95% were unaware of existing guidelines [9]. There is a clear need for a national evidence-based clinical guideline for foot health that is aimed at clinicians and focused on IA more widely.

This new BSR guideline will address the assessment and management of foot health in adults, children and young people with IA and will focus specifically on the healthcare setting in the UK. Clear, culturally sensitive guidance regarding evidence-based strategies for the management of foot problems in people with IA will help all clinicians to provide high-quality care for their patients, service providers, and commissioners, to ensure that adequately resourced foot health services are available to meet the needs of patients. The guideline will provide advice to enable a range of clinicians to provide first-line therapy for foot conditions where access to podiatry is limited, and advise when specialist opinions should be sought.

Key facts and figures

IA is an umbrella term encompassing a range of chronic, autoimmune conditions characterised by joint inflammation. These include RA, JIA and spondyloarthropathy (SpA) – which encompasses PsA, AS, reactive arthritis, enteropathic arthritis and undifferentiated SpA.

Despite the introduction of aggressive pharmacological therapies, foot problems frequently occur in IA. Around 90% of people with RA experience foot problems during the course of the disease, including rearfoot and forefoot deformity, tibialis posterior dysfunction, peripheral arthritis, and subluxation and dislocation of the MTP joints, leading to pain and reduced walking ability [10]. The foot is also particularly susceptible to damage in JIA. Foot-related impairment and disability has been shown to persist in over 90% of children and young people with the condition, despite intensive pharmacological therapy [11], and foot problems are also common in adults with JIA. In SpA, foot problems also include peripheral arthritis, dactylitis and enthesitis, particularly at the Achilles tendon, plantar fascia and tibialis posterior tendon insertions but also at many other sites. In PsA specifically, forefoot deformity affects over 90% of people with the condition, while almost two-thirds experience foot pain [12].

Other extra-articular features of IA can manifest in the foot, including peripheral neuropathy and entrapment neuropathies. The risk of peripheral arterial disease is also increased in IA, particularly amongst individuals with a history of steroid use [13]. Long-term steroid use can also contribute to poor tissue viability in the foot, and when combined with joint deformity and poor vascular supply, the risk of tissue breakdown is significantly increased. Foot ulcers are common in IA [14, 15], and in immunosuppressed patients these carry an increased risk of potentially serious infection.

Despite significant advances in the pharmacological management of IA with the advent of whole new classes of medication and a new treatment paradigm, foot problems persist. The impact of foot damage in IA is often underestimated [16] and trivialized, yet people with foot problems consistently report marked reduction in their quality of life, indicating that the impact of foot disorders extends well beyond localized pain and discomfort [17].

Current practice

A person with IA might present to primary or secondary care with foot problems. In some cases, foot problems precede the diagnosis of IA; 31% of cases are known to have had their first IA symptoms in their feet [18]. After diagnosis, foot problems may be monitored as part of the assessment of overall prognosis and disease activity, potentially with follow-up imaging. Some units run multidisciplinary clinics, but more commonly people with foot problems are seen separately by rheumatology and podiatry, sometimes with additional input from physiotherapy, orthotics, occupational therapy or orthopaedic surgery. The presentation of foot problems in IA is diverse, with some people experiencing problems with general nail and skin care, whereas others have pain and change in foot shape and posture (deformity), making it difficult to walk and find suitable footwear. Such problems can have specific challenges for children and young people as their musculoskeletal system is growing and developing. Others may present with neurological or vascular disease affecting the feet, or with foot ulcers. Treatments for foot pain and deformity can include general nail care, callus debridement, foot orthoses, footwear advice and provision, stretching and strengthening exercises, lifestyle advice and surgery. People with persistent active inflammation in the foot may benefit from corticosteroid injections or a change in systemic treatment.

Variation in practice is widespread and the inadequacies of foot care in the UK are well documented. Although National Early Inflammatory Arthritis Audit (NEIAA) data indicated that 76% of rheumatology departments had podiatry access in 2020 [19], a 2021 BSR rheumatology workforce report highlighted that 80% of departments do not have a podiatrist embedded in their multidisciplinary team [20]. Additionally, a recent clinical audit into the adherence of foot health management standards of RA across six National Health Service

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(NHS) Trusts found that only one podiatry department had the facility to see people with RA within six weeks of their initial diagnosis [21], while cross-sectional and longitudinal cohort studies in secondary care frequently report that only 30% to 40% of people with RA access any form of professional foot care or surgery [22–24].

It has been suggested that better integration of foot health services into rheumatology would be beneficial for people with IA [25]. Referral pathways are often unclear, and the lack of podiatrists within specialist teams means many patients seek foot care from the independent sector or non-specialist podiatrists who may not have the specific knowledge to manage their problems. Poor compliance with current foot health standards amongst podiatry departments is prevalent [21].

2 Who the guideline is for

This guideline is for

- rheumatologists, general practitioners, orthopaedic surgeons, allied health professionals, and specialist rheumatology nurses involved in the management of people with foot problems in IA;
- people with foot problems in IA and their carers.

Equality considerations

- none known.

3 What the guideline will cover

3.1 Who is the focus?

Groups that will be covered

- Adults with IA affecting the foot;
- Children and young people with IA affecting the foot.

3.2 Settings

Settings that will be covered

- Primary care and community settings;
- Secondary and tertiary care settings.

3.3 Activities, services or aspects of care

Key areas that will be covered

We will look at evidence in the areas below when developing the guideline, but it may not be possible to make recommendations in all the areas.

Treatment of people

Foot problems (including pain, deformity, nail and skin pathologies, ulceration, reduced circulation and neuropathy) in people with the following rheumatic diseases:

- RA;
- SpA, including PsA, AS, enteropathic arthritis, reactive arthritis and undifferentiated SpA;
- JIA.

Assessment and diagnosis

- Assessments;
- Imaging;
- Referral to specialist foot services.

Treatment strategy

- personalized care;
- orthotic devices;
- footwear;
- targeted exercises and gait rehabilitation;
- nail and skin care;
- wound management;
- targeted injection therapy;
- reviewing systemic disease control;
- surgical referral;
- follow-up and monitoring.

Secondary prevention

- physical activity;
- smoking;
- weight loss.

Areas that will not be covered

- Surgical procedures;
- Treatment of traumatic foot injuries;
- Systemic drug therapy.

Related guidance

- The North West Podiatry Services Clinical Effectiveness Group's 2010 rheumatology guidelines for the management of foot health for people with rheumatoid arthritis [5];
- NICE guideline [NG100] for rheumatoid arthritis in adults: management in 2018 [6];
- ARMA Standards of Care for People with Musculoskeletal Foot Health Problems in 2008 [7];
- ARMA Standards of Care for Children and Young People with Juvenile Idiopathic Arthritis in 2010 [8].

3.4 Key issues and draft questions

While writing this scope, we have identified the following key issues and draft questions related to them. The key issues and draft questions will be used to develop more detailed review questions, which guide the systematic review of the literature.

Assessment and diagnosis

Assessments

1. In adults or children and young people with suspected or confirmed IA, what clinical assessments should be undertaken when assessing foot health and disease activity, and how often?

Imaging

2. In adults or children and young people with suspected or confirmed IA, what imaging should be requested

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when assessing foot health, and when should imaging be requested?

Referral to specialist foot services

3. When should adults or children and young people with suspected or confirmed IA be referred to specialist foot services, e.g. podiatry?

Treatment strategy

Personalised care

4. In adults or children and young people with foot problems in IA, what personalised care (e.g. support for self-management, activation, shared decision making and culturally-sensitive education) relating to foot health, and considering a person's wider biopsychosocial health determinants, should be provided and when?

Orthotic devices

5. In adults or children and young people with foot problems in IA, are orthotic devices effective, when are they indicated, and which types of orthotic devices are effective?

Footwear

6. In adults or children and young people with foot problems in IA, what types of footwear are effective?

Targeted exercises, gait rehabilitation and electrophysical therapies

7. In adults or children and young people with foot problems in IA, what frequency, intensity, type and time (duration) of exercises, gait rehabilitation and electrophysical therapies is effective?

Nail and skin care

8. In adults or children and young people with common toenail pathologies in IA, what conservative treatments are effective, and when should abnormal nails be surgically removed?
9. In adults or children and young people with common skin pathologies (e.g. callus) in IA, what treatments are effective?

Wound management

10. In adults or children and young people with foot ulceration in IA, including infected foot ulcers, what treatments are effective?

Targeted injection therapy

11. In adults or children and young people with foot problems in IA, are local corticosteroid injections safe and effective, and if so, when should these be offered?

Reviewing systemic disease control

12. When should local foot symptoms prompt a review of systemic disease control in adults or children and young people with IA?

Surgical referral

13. In adults or children and young people with foot problems in IA, when should a surgical referral be considered?
14. In patients requiring foot and ankle surgical procedures, including nail surgery, should biologics/DMARDs be stopped, when should they be stopped, and for how long?

Follow-up and monitoring

15. How often should foot health be reassessed in adults or children and young people with IA?
16. In young people with IA who are transitioning from paediatric to adult care, how should foot health be incorporated?

Secondary prevention

Physical activity

17. In adults or children and young people with foot problems in IA, what is the clinical effectiveness of physical activity?

Smoking

18. In adults or children and young people with foot problems in IA who smoke, what is the clinical effectiveness of giving up smoking?

Weight loss

19. In adults or children and young people with foot problems in IA who are overweight or obese, what is the clinical effectiveness of weight loss?

The guideline is expected to be published in 2023.

4 Guideline working group constituency

Edward Roddy (WG lead) – Rheumatologist
Mike Backhouse (WG deputy lead) – Podiatrist
Lara Chapman (lead author) – Podiatrist
Louise Warburton – GP
Jasmine Davey – Lay member
Alan Rawlings – Lay member
Susan Varley – Lay member
Adele Whitgreave – Lay member
Adam Lomax – Orthopaedic foot/ankle surgeon
Rob Rees – Orthopaedic foot/ankle surgeon
Robbie Rooney – Orthotist
Rachel Ferguson – Paediatric Podiatrist
Gavin Cleary – Paediatric Rheumatologist
Lindsay Bearne – Physiotherapist
Lindsey Cherry – Podiatrist
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Lucy Saunders – Podiatrist
Heidi Siddle – Podiatrist
Jim Woodburn – Podiatrist
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Funding: This work was supported by the British Society for Rheumatology.

Disclosure statement: L.W. has received payment from Novartis for an online lecture. No other authors have conflicts of interest to declare.

Data availability statement

No new data were generated or analysed in support of this research.

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Arthritis & Rheumatology
Vol. 74, No. 3, March 2022, pp 386–392
DOI 10.1002/art.41982
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2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis With Polyangiitis

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European Alliance of Associations for Rheumatology (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

The ACR is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.

Objective. To develop and validate revised classification criteria for eosinophilic granulomatosis with polyangiitis (EGPA).

Methods. Patients with vasculitis or comparator diseases were recruited into an international cohort. The study proceeded in 5 phases: 1) identification of candidate criteria items using consensus methodology, 2) prospective collection of candidate items present at the time of diagnosis, 3) data-driven reduction of the number of candidate items, 4) expert panel review of cases to define the reference diagnosis, and 5) derivation of a points-based risk score for disease classification in a development set using least absolute shrinkage and selection operator logistic regression, with subsequent validation of performance characteristics in an independent set of cases and comparators.

Results. The development set for EGPA consisted of 107 cases of EGPA and 450 comparators. The validation set consisted of an additional 119 cases of EGPA and 437 comparators. From 91 candidate items, regression analysis identified 11 items for EPGA, 7 of which were retained. The final criteria and their weights were as follows: maximum eosinophil count ≥1 × 10^9/liter (+5), obstructive airway disease (+3), nasal polyps (+3), cytoplasmic antineutrophil cytoplasmic antibody (ANCA) or anti–proteinase 3 ANCA positivity (−3), extravascular eosinophilic predominant inflammation (+2), mononeuritis multiplex/motor neuropathy not due to radiculopathy (+1), and hematuria (−1). After excluding mimics of vasculitis, a patient with a diagnosis of small- or medium-vessel vasculitis could be classified as having EGPA if the cumulative score was ≥6 points. When these criteria were tested in the validation data set, the sensitivity was 85% (95% confidence interval [95% CI] 77–91%) and the specificity was 99% (95% CI 98–100%).

Conclusion. The 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for EGPA demonstrate strong performance characteristics and are validated for use in research.

This article is published simultaneously in the March 2022 issue of *Annals of the Rheumatic Diseases*.

The Diagnostic and Classification Criteria in Vasculitis (DCVAS) study, of which the development of these classification criteria was a part, was funded by grants from the American College of Rheumatology (ACR), the European Alliance of Associations for Rheumatology (EULAR), the Vasculitis Foundation, and the University of Pennsylvania Vasculitis Center.

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INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a form of vasculitis that is histologically defined by eosinophil-rich, necrotizing granulomatous inflammation primarily involving the respiratory tract, along with necrotizing vasculitis of small- to medium-sized arteries (1). EGPA is considered a form of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV), along with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). ANCAs are detected in ~40–60% of patients with EGPA and are typically directed against myeloperoxidase (MPO) (2,3).

In 1990, the American College of Rheumatology (ACR) published classification criteria for EGPA (4). By current standards, these criteria have never been validated because they were developed using data from only 20 patients with EGPA without independent test and validation sets. Furthermore, the criteria were derived by comparing clinical data from patients with EGPA to data from 787 patients with other forms of vasculitis. Many of these comparators were patients with giant cell arteritis, a form of large-vessel vasculitis that is typically not difficult to readily distinguish from EGPA based on obvious clinical differences. Despite these methodologic weaknesses, the 1990 ACR criteria for EGPA have existed unchanged for several decades and have been useful to advance clinical research in these diseases. This article outlines the development and validation of the new ACR/European Alliance of Associations for Rheumatology (EULAR)–endorsed classification criteria for EGPA.

METHODS

A detailed and complete description of the methods involved in the development and validation of the classification criteria for EGPA is provided in Supplementary Appendix 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract. Briefly, an international Steering Committee comprising clinician investigators with expertise in vasculitis, statisticians, and data managers was established to oversee the overall Diagnostic and Classification Criteria in Vasculitis (DCVAS) project (5). The Steering Committee established a 5-stage plan using data-driven and consensus methodology to develop the criteria for each of 6 forms of vasculitis.

Stage 1: generation of candidate classification items for the systemic vasculitides. Candidate classification items were generated by expert opinion and reviewed by a group of vasculitis experts across a range of specialties using a nominal group technique.

Stage 2: DCVAS prospective observational study. A prospective, international, multisite observational study was conducted (see Appendix A for study investigators and sites). Ethical approval was obtained from national and local ethics committees. Consecutive patients representing the full spectrum of disease were recruited from academic and community practices. Patients were included if they were 18 years or older and had a diagnosis of vasculitis or a condition that mimics vasculitis. Patients with AAV could only be enrolled within 2 years of diagnosis. Only data present at diagnosis were recorded.

Stage 3: refinement of candidate items specifically for AAV. The Steering Committee conducted a data-driven process to reduce the number of candidate items of relevance to cases and comparators for AAV. Items were selected for exclusion if they had a prevalence of <5% within the data set and/or they were not clinically relevant for classification criteria (e.g., related to infection, malignancy, or demographic characteristics). Low-frequency items of clinical importance could be combined, when appropriate.

Stage 4: expert review to derive a gold standard–defined final set of cases of AAV. Experts in vasculitis from a wide range of geographic locations and specialties reviewed all submitted cases of vasculitis and a random subset of mimics of vasculitis. Each reviewer was asked to review ~50 submitted cases to confirm the diagnosis and to specify the certainty of their diagnosis as follows: very certain, moderately certain, uncertain, or very uncertain. Only cases agreed upon with at least moderate certainty were retained for further analysis.

Stage 5: derivation and validation of the final classification criteria for EGPA. The DCVAS AAV data set was randomly split into development (50%) and validation (50%) sets. Comparisons were performed between cases of EGPA and a comparator group randomly selected from the DCVAS cohort in the following proportions: another type of AAV (including GPA and MPA), 60%; another form of small-vessel vasculitis (e.g., cryoglobulinemic vasculitis) or medium-vessel

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fart.41982&file=art41982-sup-0001-Disclosureform.pdf.

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Submitted for publication February 28, 2020; accepted in revised form September 21, 2021.

vasculitis (e.g., polyarteritis nodosa), 40%. Least absolute shrinkage and selection operator (lasso) logistic regression was used to identify items from the data set and create a parsimonious model including only the most important items. The final items in the model were formulated into a clinical risk-scoring tool with each factor assigned a weight based on its respective regression coefficient. A threshold that best balanced sensitivity and specificity was identified for classification.

In sensitivity analyses, the final classification criteria were applied to an unselected population of cases and comparators from the DCVAS data set based on the submitting physician diagnosis. Comparison was also made between the measurement properties of the new classification criteria for EGPA and the 1990 ACR classification criteria for EGPA using pooled data from the development and validation sets.

RESULTS

Generation of candidate classification items for the systemic vasculitides. The Steering Committee identified >1,000 candidate items for the DCVAS case report form (see Supplementary Appendix 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract).

DCVAS prospective observational study. Between January 2011 and December 2017, the DCVAS study recruited 6,991 participants from 136 sites in 32 countries. Information on the DCVAS sites, investigators, and participants is listed in Supplementary Appendices 3, 4, and 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract.

Refinement of candidate items specifically for AAV. Following a data-driven and expert consensus process, 91 items from the DCVAS case report form were retained for regression analysis, including 45 clinical (14 composite), 18 laboratory (2 composite), 12 imaging (all composite), and 16 biopsy (1 composite) items. Some clinical items were removed in favor of similar but more specific pathophysiologic descriptors. For example, "Hearing loss or reduction" was removed, and the composite item "Conductive hearing loss/sensorineural hearing loss" was retained. See Supplementary Appendix 6, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract, for the final candidate items used in the derivation of the classification criteria for GPA, MPA, and EGPA.

Expert review to derive a gold standard–defined final set of cases of AAV. Fifty-five independent experts reviewed vignettes derived from the case report forms for 2,871 cases submitted with a diagnosis of either small-vessel vasculitis (90% of case report forms) or another type of vasculitis or a mimic of vasculitis (10% of case report forms). The characteristics of the expert reviewers are shown in Supplementary Appendix 7, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract. A flow chart showing the results of the expert review process is shown in Supplementary Appendix 8, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract. A total of 2,072 cases (72%) passed the process and were designated as cases of vasculitis; these cases were used for the stage 5 analyses.

After expert panel review, 226 of 315 cases of EGPA were retained for subsequent analysis. Compared to patients who were retained, patients who were excluded from further analysis

Table 1. Demographic and disease features of cases of EGPA and comparators*

	EGPA (n = 226)	Comparators (n = 887)†	*P*
Age, mean ± SD years	52.9 ± 14.4	56.2 ± 17.6	0.009
Sex, no. (%) female	113 (50.0)	445 (50.2)	1.000
Maximum serum creatinine, mean ± SD			<0.001
μmoles/liter	85.0 ± 53.6	205.90 ± 237.0	
mg/dl	0.96 ± 0.6	2.33 ± 2.7	
cANCA positive, no. (%)	17 (7.5)	251 (28.3)	<0.001
pANCA positive, no. (%)	83 (36.7)	289 (32.6)	0.271
Anti–PR3-ANCA positive, no. (%)	7 (3.1)	264 (29.8)	<0.001
Anti–MPO-ANCA positive, no. (%)	98 (43.4)	323 (36.4)	0.065
Maximum eosinophil count ≥1 × 10^9/liter, no. (%)	208 (92.0)	53 (6.0)	<0.001

* cANCA = cytoplasmic antineutrophil cytoplasmic antibody; pANCA = perinuclear ANCA; anti–PR3-ANCA = anti–proteinase 3–ANCA; anti–MPO-ANCA = anti–myeloperoxidase-ANCA.
† Diagnoses of comparators for the classification criteria for eosinophilic granulomatosis with polyangiitis (EGPA) included granulomatosis with polyangiitis (n = 300), microscopic polyangiitis (n = 291), polyarteritis nodosa (n = 51), non–ANCA-associated small-vessel vasculitis that could not be subtyped (n = 51), Behçet's disease (n = 50), IgA vasculitis (n = 50), cryoglobulinemic vasculitis (n = 34), ANCA-associated vasculitis that could not be subtyped (n = 25), primary central nervous system vasculitis (n = 19), and anti–glomerular basement membrane disease (n = 16).

had significantly higher serum creatinine levels (mean ± SD 102.8 ± 88.7 versus 85.0 ± 53.6 μmoles/liter; $P = 0.03$), lower rates of MPO-ANCA positivity (22% versus 43%; $P < 0.01$), and were less likely to have maximum eosinophil counts ≥1 × 10^9/liter (62% versus 92%; $P < 0.01$). There were 887 comparators randomly selected for analysis. Table 1 shows the demographic and disease features of the 1,113 cases included in this analysis (226 patients with EGPA and 887 comparators), of which 557 (50%;107 patients with EGPA and 450 comparators) were in the development set, and 556 (50%; 119 patients with EGPA and 437 comparators) were in the validation set.

Derivation and validation of the final classification criteria for EGPA. Lasso regression of the previously selected 91 items yielded 11 independent items for EGPA (Supplementary Appendix 9A, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract). Each item was then adjudicated by the DCVAS Steering Committee for inclusion based on clinical relevance and specificity to EGPA, resulting in 7 final items. Weighting of an individual criterion was based on logistic regression fitted to the 7 selected items (see Supplementary Appendix 10A, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract).

Model performance. Use of a cutoff of ≥6 for total risk score (see Supplementary Appendix 11A, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract, for different cut points) yielded a sensitivity of 84.9% (95% confidence interval [95% CI] 77.2–90.8%) and a specificity of 99.1% (95% CI 98.3–99.8%) in the validation set. The area under the curve (AUC) for the model was 0.98 (95% CI 0.97–1.00) in the development set and 0.99 (95% CI 0.97–1.00) in the validation set for the final EGPA classification criteria (Supplementary Appendix 12A, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract).

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

CLASSIFICATION CRITERIA FOR EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify a patient as having eosinophilic granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

CLINICAL CRITERIA

Obstructive airway disease	+3
Nasal polyps	+3
Mononeuritis multiplex	+1

LABORATORY AND BIOPSY CRITERIA

Blood eosinophil count ≥ 1 x10^9/liter	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-3
Hematuria	-1

Sum the scores for 7 items, if present. A score of ≥ 6 is needed for classification of EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS.

Figure 1. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis.

The final classification criteria for EGPA are presented in Figure 1 (for the slide presentation version, see Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41982/abstract).

Sensitivity analyses. The classification criteria for EGPA were applied to 2,871 patients in the DCVAS database using the original physician-submitted diagnosis (n = 315 EGPA and 2,556 randomly selected comparators). Use of the same cut point of ≥6 points for the classification of EGPA yielded a similar specificity of 99% but a lower sensitivity of 75%. This upheld the a priori hypothesis that specificity would remain unchanged but sensitivity would be reduced in a population of patients that included fewer clearcut diagnoses of EGPA (i.e., cases that did not pass expert panel review).

When the 1990 ACR classification criteria for EGPA were applied to the DCVAS data set, the criteria performed poorly due to low sensitivity (44%) but retained excellent specificity (99%), with an AUC of 0.72 (95% CI 0.68–0.75).

DISCUSSION

Presented here are the final 2022 ACR/EULAR EGPA classification criteria. A 5-stage approach has been used, underpinned by data from the multinational prospective DCVAS study and informed by expert review and consensus at each stage. The comparator group for developing and validating the criteria were patients with other forms of AAV and other small- and medium-vessel vasculitides, which are the clinical entities where discrimination from EGPA is difficult, but important. The new criteria for EGPA have excellent sensitivity and specificity and incorporate ANCA testing. The criteria were designed to have face and content validity for use in clinical trials and other research studies.

These criteria are validated and intended for the purpose of *classification* of vasculitis and are not appropriate for use in establishing a *diagnosis* of vasculitis. The aim of the classification criteria is to differentiate cases of EGPA from similar types of vasculitis in research settings. Therefore, the criteria should only be applied when a diagnosis of small- or medium-vessel vasculitis has been made and all potential "vasculitis mimics" have been excluded. The exclusion of mimics is a key aspect of many classification criteria, including those for Sjögren's syndrome (6) and rheumatoid arthritis (7). The 1990 ACR classification criteria for vasculitis perform poorly when used for diagnosis (i.e., when used to differentiate between cases of vasculitis versus mimics without vasculitis) (8), and it is expected that the 2022 criteria would also perform poorly if used inappropriately as diagnostic criteria in people in whom alternative diagnoses, such as infection or other non-vasculitis inflammatory diseases, are still being considered. Specifically, the criteria were not developed to differentiate patients with EGPA from those with other related hypereosinophilic syndromes or eosinophilic malignancies (9).

The 2022 ACR/EULAR EGPA classification criteria reflect the collaborative effort of the international vasculitis community to delineate the salient clinical features that differentiate EGPA from other forms of vasculitis. The final criteria include 7 clinical items that are easily assessed during routine clinical evaluation of patients with EGPA. The criteria highlight the importance of blood eosinophilia, asthma, and eosinophilic inflammation to classify EGPA among other forms of vasculitis and specify additional features (e.g., nasal polyps, mononeuritis multiplex) that function as important disease classifiers. Classification criteria are intended to define a homogeneous group of patients with a particular disease for inclusion into clinical research studies. By maximizing specificity, the revised criteria for EGPA ensure that few cases will inappropriately meet the criteria threshold of ≥6 points; thus, these criteria will function to facilitate the conduct of future clinical trials and other studies in EGPA.

The negative items included in the final criteria underscore that these criteria are intended for use as classification, not diagnostic, criteria to differentiate EGPA from other forms of vasculitis in research settings. Both hematuria and anti–proteinase 3 ANCA (anti–PR3-ANCA) function as negative items in the new EGPA classification criteria, yet glomerulonephritis and ANCA are features of disease that, when present, can be useful to diagnose EGPA. When compared to other forms of AAV, however, biopsy-proven glomerulonephritis was significantly less common in the DCVAS cohort in patients with EGPA (4.9%) compared to those with GPA (27.8%) or MPA (48.5%). Similarly, anti–PR3-ANCAs have been reported in few patients with EGPA but are much more prevalent in GPA (10). For these reasons, hematuria and anti–PR3-ANCAs work against a patient with small-vessel vasculitis being classified as having EGPA. Although anti–MPO-ANCAs can be detected in 40–60% of patients with EGPA, anti–MPO-ANCA positivity was not included in the final criteria because these antibodies are significantly more prevalent in diseases like MPA and thus are not discriminant classifiers for EGPA (11).

There are some study limitations to consider. Although this was the largest international study ever conducted in vasculitis, most patients were recruited from Europe, Asia, and North America. The performance characteristics of the criteria should be further tested in African and South American populations, which may have different clinical presentations of vasculitis. These criteria were developed using data collected from adult patients with vasculitis. Although the clinical characteristics of EGPA and the other vasculitides which these criteria were tested against are not known to differ substantially between adults and children, these criteria should be applied to children with some caution. The scope of the criteria is intentionally narrow and applies only to patients who have been diagnosed as having vasculitis. Diagnostic criteria are not specified. The criteria are intended to identify homogeneous populations of disease and, therefore, may not be appropriate for studies focused on the full spectrum of clinical heterogeneity in these conditions. To maximize relevance and face

validity of the new criteria, study sites and expert reviewers were recruited from a broad range of countries and different medical specialties. Nonetheless, the majority of patients were recruited from academic rheumatology or nephrology units, which could have introduced referral bias.

There are several strengths to the new 2022 ACR/EULAR EGPA classification criteria. The criteria were developed within a large cohort reflecting international expertise in systemic vasculitis according to ACR guidance for classification criteria development (11). The criteria represent several important methodologic advancements compared to the original 1990 ACR classification criteria for EGPA. Expert review rather than submitting physician diagnosis was used as the diagnostic reference standard to minimize investigator bias. Second, while the 1990 ACR criteria were entirely derived in 20 patients with EGPA and not validated, the new criteria were developed in 107 patients with EGPA and validated in an independent test set that contained an additional 119 patients with EGPA. Third, unlike the 1990 ACR criteria, the new ACR/EULAR EGPA criteria are weighted to reflect the relative importance of specific items (e.g., eosinophil counts). Finally, when both criteria sets were tested within the DCVAS cohort, the performance characteristics of the 1990 ACR criteria were suboptimal when compared to the 2022 revised ACR/EULAR EGPA criteria.

The 2022 ACR/EULAR classification criteria for EGPA are the product of a rigorous methodologic process that utilized an extensive data set generated by the work of a remarkable international group of collaborators. These criteria have been endorsed by the ACR and EULAR and are now ready for use to differentiate one type of vasculitis from another to define populations in research studies.

ACKNOWLEDGMENTS

We acknowledge the patients and clinicians who provided data to the DCVAS project.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Merkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 57, No. 2, March 15, 2007, pp 193–202
DOI 10.1002/art.22552
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SPECIAL ARTICLE

A Proposed Revision to the ACR20: The Hybrid Measure of American College of Rheumatology Response

AMERICAN COLLEGE OF RHEUMATOLOGY COMMITTEE TO REEVALUATE IMPROVEMENT CRITERIA

Objective. **Although use of the American College of Rheumatology 20% improvement criteria (ACR20) has standardized response measurement in rheumatoid arthritis (RA) trials, the ACR20 has been criticized as less sensitive to change than are continuous measures of response, and its threshold for response (≥20%) is thought to be low. Our goal was to redefine response in RA in a manner that 1) corresponds to a clinical impression of response (clinical validity), 2) maximizes sensitivity to change, and 3) allows for calculation of the ACR20 to continue standardization of reporting.**

Methods. **We examined multiple different ways of defining response, including dichotomous definitions (patient improved versus not improved), ordinal definitions (degree of response scored on an ordinal scale), disease activity indexes, continuous definitions, and definitions that were hybrids of continuous and ordinal measures. Candidate definitions included the ACR20, ACR50, ACR70, the Disease Activity Score, the Simplified Disease Activity Index, the ACR-N, the nACR, and the European League Against Rheumatism (EULAR) response. We also tested variations on these approaches. To test clinical validity, we administered a survey involving patients from a previous trial who had various levels of improvement and asked rheumatologists whether and by how much these patients improved. To determine sensitivity to change, we collected data from 11 large multicenter trials of disease-modifying antirheumatic drugs (DMARDs) in RA comprising 3,665 patients (7 anti–tumor necrosis factor α arms, 4 conventional DMARD arms, 2 biologic arms) and ranked candidate definitions of response according to their average *P* value across trials in distinguishing active treatment from placebo or combination therapy versus single-drug therapy.**

Results. **All 135 tested measures had clinical validity based on survey responses, although dichotomous measures did not capture the range of responses (e.g., the ACR20 did not capture the extra clinical improvement between the ACR20 and the ACR50). In trial analyses, continuous measures had the best sensitivity to change. Among the best scoring measures was a hybrid measure that retained information on the ACR20, ACR50, and ACR70 and combined that with the mean percent improvement in core set measures. When comparing 2 treatments, this hybrid measure had an average *P* value much lower than that for the ACR20. If a trial needed 200 patients to have 80% power (2-sided $\alpha = 0.05$) to detect a difference between treatments if it used the ACR20, the same trial would need 108 patients if the hybrid measure were used.**

Conclusion. **We suggest use of a new hybrid measure of RA response that maximizes sensitivity to change, correlates well with rheumatologists' impressions of improvement, and preserves the ACR20.**

KEY WORDS. Rheumatoid arthritis; Trials; Outcome measures.

INTRODUCTION

Before the 1990s, reports of rheumatoid arthritis (RA) trials cited multiple primary outcomes, often with little overlap of measures from trial to trial. This made it nearly impossible to evaluate whether therapies that produced 1 or 2 positive outcomes actually demonstrated treatment effi-

Supported by grants from the American College of Rheumatology and by the NIH (grant AR-47785).

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Dr. Bombardier has received consulting fees (less than $10,00 each) from Abbott, Amgen, AstraZeneca, Bayer, Inc., Bristol-Myers Squibb Canada Company, Hoffmann-la Roche, Pfizer, Roche Products, Schering Canada, Solvay Pharma, and Wyeth-Ayerst Research, is a member of the Advisory Board and has received consulting fees (more than $10,000) for Merck & Company, and holds research grants

cacy; it also created a formidable barrier to the comparison of treatments. This situation changed with the development of the American College of Rheumatology (ACR) core set of disease activity measures (1,2). The core set required the inclusion of 7 clinical end points for all RA trials: swollen joint count, tender joint count, physician's assessment of disease activity, patient's assessment of disease activity, patient's assessment of pain, and patient's assessment of physical function, and levels of an acute-phase reactant (either the C-reactive protein [CRP] level or the erythrocyte sedimentation rate [ESR]). The core set measures still constituted 7 outcome measures, without a single primary measure.

In the early 1990s, an ACR committee used the core set to develop a single measure of improvement, the ACR preliminary criteria for improvement in RA (ACR20) (3). An ACR20 response was defined as at least 20% improvement in both the tender joint count and the swollen joint count and at least 20% improvement in 3 of the 5 other core set measures listed above.

Adoption of the ACR20 (and promulgation of a similar definition of improvement by the European League Against Rheumatism [EULAR]) (4) represented a substantial advance in measuring clinical responses in rheumatology. Trials almost immediately became standardized, with most using the ACR20 as their primary outcome measure. Investigators, appropriately or not, began to compare ACR20 response rates between therapies, and response measures were defined for other rheumatic diseases. The ACR20 also became the primary outcome used by the US Food and Drug Administration (FDA) to evaluate new treatments for RA. The ACR20 focused on improvement in individual patients rather than the mean improvement in groups of treated patients, permitting investigation of why the response to treatment of individual patients differed (5).

Widespread use of the ACR20 highlighted flaws that were not noted during its development. First, as therapies improved, 20% improvement seemed like a low bar, and trials began to incorporate other thresholds for improvement such as the ACR50 and the ACR70. Second, the ACR20 was a dichotomous measure of individual response (i.e., response was either present or absent). However, incorporating information about the relative improvement among patients in a trial would not only be more informative, it would also increase the sensitivity to change of the response definition, making it easier to compare treatments. Furthermore, although the ACR20 measure was used widely, it was not used consistently. Some studies required an ACR20 response only at the end of the trial, other studies used maximal improvement at any time during the trial, and still others prespecified an area under the curve approach to the ACR20. The diversity of ways in which the ACR20 was used led to problems comparing results between trials.

Of these concerns, the main one focused on the realization that the ACR20 measure was not as sensitive to change as other, more continuously defined measures of improvement (6). For example, the ACR-N (a continuous outcome defined by the percent improvement in either the tender joint count, the swollen joint count, or 5 other outcomes) was proposed as being an improvement of the ACR20 (7), as was a definition that simply counted the number of core set measures that improved by at least 20%, the nACR. Although each of these alternatives offered advantages and disadvantages to the ACR20, it became obvious that a revision to the ACR20, with attention to its sensitivity to change, was needed. Two emerging changes in RA trials further motivated a modification of the ACR20: 1) increasing difficulty recruiting patients for trials, requiring an outcome measure that would limit sample size requirements, and 2) the availability of many new effective treatments whose comparative efficacy would not be evaluable without a new, more precise measure.

Two other challenges accompanied revision of the ACR20. Because the ACR20 is widely known and has become a standard way of communicating response rates, any new measure should be built on the ACR20 as much as possible. Also, any new measure must correlate with clinicians' impressions of improvement. With all of these sometimes conflicting goals, we set about to reevaluate the definition of response in RA trials.

METHODS

The approach we used to reevaluate improvement criteria was as follows:

1. Identify potential candidate measures of response, trying to be as comprehensive as possible. We considered all commonly used or proposed measures plus variations of these.

from Abbott Laboratories, Schering Canada, Pfizer, and BMS. Dr. Bathon has received consulting fees and/or honoraria (less than $10,000 each) from Wyeth and Centocor, and has contracts with Amgen, Biogen-Idec, Bristol Myers, Roche, and Rinat. Dr. Choi has received grant support from TAP Pharmaceuticals and serves on advisory boards for TAP and Savient Pharmaceuticals. Dr. Simon is a consultant for AAI Pharma, Abbott, Affinergy, Astrazeneca, Abraxxis, Alpha Rx, Avanir, Nuvo/Dimethaid, Neopharm, Novartis, Pfizer, Plx Pharma, Hisamatsu, LAB Pharma, Dr Reddys, Biosense, Cerimon, Leerink Swann, Alimera, Nomura, Luxor, Paraexel, Nitec, Bayer, Combinatoryx, Rigel, Chelsea, Regeneron, Genelabs, Cypress, SNBL, Skyepharma, Solace, Puretchventures, Puretch Development, Whit Mountain Pharma, TAP, Cell Therapeutics, Omeros, Jazz, Schwarz, Proethic, Takeda, Teva, Zydus, Proprius, Savient, Alder, Cure, Cellegy, Chemocentryx, McKesson, Diobex, Sepracor, Purdue, Serono, Coley, Mediimune, Altea, Neuromed, Polymerix, Talagen, and Tigenix. Dr. Tugwell has received consulting fees from Abbott, Almirall, Astra Zeneca, Aventis, Berlex, Biomatrix, Bristol-Myers Squibb, Cadeuceus Group, Centocor, Dimedix, Dimethaid, Eli Lilly, Glaxo-Welcome, Glaxo Smith Kline, Hoechst Marion Roussel, Innovus, Johnson & Johnson, Lilly Research, Medicine Group, Medicus, Merck, Merck Frosst, Novartis, Novopharm, Ortho-McNeil, Pennside, Roche, Sandoz, Scios, Searle, and Wyeth Ayerst, and organizes a biannual outcome measures consensus meeting (Outcome Measures in Rheumatology [OMERACT]), which has received financial support from numerous pharmaceutical companies. Dr. White is a past employee of Amgen, owns stock in Amgen, and has stock options in Medimmune.

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Submitted for publication August 30, 2006; accepted in revised form September 26, 2006.

2. Determine the clinical construct validity of candidate measures. We created a survey of "paper" patients from a large anti–tumor necrosis factor (anti-TNF) trial and asked rheumatologist respondents which patients in this trial had improved and by how much. We correlated survey responses on the degree of patient improvement with the amount of response determined by candidate measures.
3. Assess the discriminant validity of candidate measures. We collected raw data from a group of large multicenter randomized trials testing second-line drug therapy in RA. We used these data to evaluate the discriminant validity (sensitivity to change) of the candidate measures.
4. Select a set of response criteria using a combination of clinical construct validity, discriminant validity, and consensus by the committee.

Step 1. Identify candidate measure. Our goal in identifying candidate measures was to be as comprehensive as possible. If we did not propose a candidate measure, it could not be ultimately selected. We used several criteria to come up with measures. We identified all currently used or recommended measures of response or disease activity in RA, including widely known measures, such as the ACR20, the ACR50, the Disease Activity Score (DAS), the Simplified Disease Activity Index (SDAI), the ACR-N, and others (Table 1). Also, we allowed for variations on these measures. For example, because some of these measures, such as the ACR20, required improvement in both the tender joint count and the swollen joint count, one variation we tested was to define response without any requirement for joint count improvement. This was called an unweighted ACR20.

We also created candidates of response that counted the number of core set measures improving. One example was the nACR (not the ACR-N), in which, for each patient, the number of core set measures that improved by ≥20% was counted. For a patient in a trial, scores for the nACR range from 0 to 7. We also tested the n2ACR, in which, for each core set measure, a patient received a score of 1 if the measure improved by ≥20% and a score of 2 if the same measure improved by 50% or more. Using the n2ACR, a patient in a trial could have a score ranging from 0 to 14.

We tested continuous measures, including the average percent improvement in all core set measures, with average defined both as the mean and the median. Other variations on this approach were evaluated.

One of the factors that has compromised the sensitivity to change of the ACR20 (8) is the requirement for improvement in the tender/swollen joint count, yet joint count improvement appears to be necessary for rheumatologists to characterize a patient as having improved (9,10). Therefore, we tested other ways of weighting joint count improvement that might not compromise sensitivity. For example, for the nACR (see above), one could doubly weight joint count improvement (i.e., ≥20% improvement in the tender or swollen joint count was counted twice, so that the nACR double-weighted score ranged from 0 to 9). Other ways of weighting joint count improvement were done in the context of new response variables (Table 1).

We created continuous measures, ordinal measures (such as the nACR), measures based on indexes of ACR activity (such as the DAS), and dichotomous measures (such as the ACR20). We also created a hybrid definition of response. A hybrid definition combines elements of 2 approaches, in this case the ACR20/50/70 approach and the continuously measured mean change in core set measures. The value of the hybrid was constrained to be within the limits of the dichotomous measures (e.g., a patient achieving ACR20 improvement but not an ACR50 response would have a hybrid score between 20 and 50. The value between 20 and 50 was determined based on the average improvement in core set measures. If a patient met the ACR50 criteria but not the ACR70 criteria, his or her score was between 50 and 70. A score of 70 or higher was defined similarly.) We tested variations on this hybrid approach, including the unweighted ACR20, ACR50, and ACR70, approaches in which the mean change was allowed to include worsening, and other approaches in which the lower limit of the score (worsening) was limited to −100 to eliminate outliers (improvement is naturally limited to +100).

Ultimately, we tested 135 candidate measures of improvement, which are listed with each of their variations in Table 1. However, presenting numeric results for all candidates involves excessive tabular data presentation. In addition, the variations on a measure performed similarly to the measure itself. Therefore, although Table 1 shows all of the candidate measures tested, we present results only for selected measures of particular interest.

Step 2. Determine clinical construct validity: the survey. To evaluate whether a candidate definition of response in RA correlated with rheumatologists' impressions of whether the patient had improved, we created a survey consisting of profiles drawn from RA patients who were receiving active treatment in a randomized trial. For each patient, we provided the values for core set measures at baseline and after 6 months of therapy (see Figure 1 for an example of a "paper" patient from the survey and the questions posed to respondents). Also, in a column after the baseline and 6-month data, we provided the percent change in each of the core set measures. For each patient, survey respondents were asked whether the patient had improved, and if respondents determined that a patient had improved, they were asked whether it was a minimal improvement, major improvement, or whether the patient's disease had gone into remission.

The paper patients chosen for the survey were selected to test the range of improvements in core set measures that might characterize different levels of clinical improvement. We selected trial patients who met criteria for ACR 0%, 10%, 20% . . . 100% improvement and varied which core set measures improved.

To examine clinical construct validity, we used rheumatologist responses to create a 4-level responder for each paper patient: no improvement, definite but not major improvement, major improvement, and remission. Using Spearman's rank correlation coefficients, we evaluated the relationship of this ordinal measure of response with the degree of response derived from each candidate measure.

Step 3. Assess the discriminant validity of candidate measures: analysis of RA trials. We collected data from 11 large, multicenter, randomized RA trials carried out

Table 1. Candidate measures of response that were evaluated

Variable name	Variable definition
O'Brien test	Nonparametric test that chooses the optimal weight for each core set measure in each trial based on the variability of the measure's score during the trial (a gold standard, not suitable for a candidate measure, but a good benchmark for comparison)
O'Brien.abs	Sum of ranks of absolute changes (ac) in all 7 core measures, where ac = final − baseline for each measure
O'Brien%	Sum of ranks of percentage changes (pc) in all 7 core measures, where for each measure pc = final − baseline/baseline
O'Brien.symm%	Sum of ranks of symmetric percentage changes (spc) in all 7 core measures, where for each measure spc = final − baseline/final + baseline
Continuous definitions of improvement*	
Percent change measures (pc)	
MeanACR	Mean % improvement in the American College of Rheumatology (ACR) 7 core set measures
ACR-N	Minimum (% tender joint count [TJC], % swollen joint count [SJC], median of other 5)
Mean3ACR	Mean (% TJC, % SJC, mean of % for other 5)
MedianACR	Median of % changes in 7 core set measures
FifthACR	Fifth highest % change
ThirdACR	Third highest % change
MeanACR2	Mean of change is all core set measures/mean of all core set measures at baseline
MeanACR3	Mean of the change in each core set measure/square root of measure score at baseline
MedianACR2	Median of change is all core set measures/median of all core set measures at baseline
MeanACR_bd	Bounded version of MeanACR, restricting worsening scores for each of 7% changes to be −100%
Symmetric percentage change measures where spc = final value − baseline value/final value + baseline value	
Meanspc	Mean symmetric % improvement
Wmeanspc	Mean of 7 with symmetric % TJC and symmetric % SJC double weighted
Medianspc	Median of 7 symmetric % changes
Disease activity indexes	
%DAS	Percentage change on DAS (Disease Activity Score)
DDAS	Absolute change on DAS
SpcDAS	Symmetric percentage change of DAS
%SDAI	Percentage change on SDAI (Simplified Disease Activity Index, Smolen)
DSDAI	Absolute change on SDAI
ODAI	For each core set measure, create ordinal scale 1,2,3,4 and average them
%ODAI	Percentage change in ODAI
DODAI	Absolute change in ODAI
EULAR	European League Against Rheumatism (EULAR) response criteria, where 0 = no response, 1 = moderate response, 2 = good response
OSDAI	SDAI cut at 10, 20 (ordinal measure 0, 1, 2 values)
DCDAI	SDAI without C-reactive protein (CRP) absolute change
%CDAI	Percentage change in CDAI (SDAI without CRP)
Pcmean	(Mean of core set measures score at end − mean of measures at start)/(mean of measures at start)
Acmean	(Mean of core set measures score at end − mean of measures at start)
Spcmean	(Mean of core set measures score at end − mean of measures at start)/(mean of measures at start + mean of measures at end)
Pcmedian	Similar to pc mean but with median replacing mean everywhere
Acmedian	Similar to ac mean but with median replacing mean everywhere
Spcmedian	Similar to spc mean but with median replacing mean everywhere
Count definitions of improvement	
nACR	nACR (number of core set measures improved by ≥20%)
nACRw	Weighted by TJC and SJC, if TJC and SJC ≥20%, nACRw = nACR, else nACRw = 0
nACRdw	Double weight of TJC and SJC
nACR50, w50, dw50	Similar as nACR-type measurements, but threshold for improvement increased to 50%
nACR70, w70, dw70	Similar as above, but threshold for improvement increased to 70%

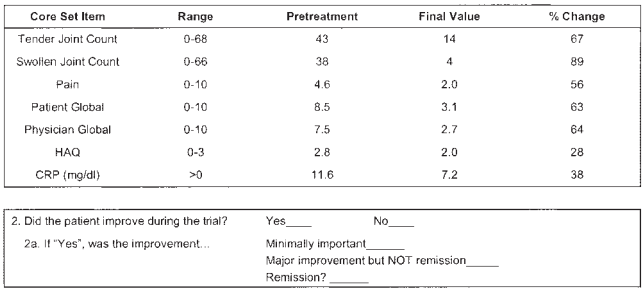
(continued)

Table 1. Candidate measures of response that were evaluated *(Continued)*

Variable name	Variable definition
n2ACR	nACR + nACR50
n2ACRw	nACRw + nACRw50
n2ACRdw	nACRdw + nACRdw50
n3ACR, w, dw	Similar as n2ACR-type measurements, but is a sum of nACR + nACR50 + nACR70 (or its variants)
Ordinal definitions of improvement	
ACRstep	0 if ACR20 = 0, 1 if ACR20 but not ACR50, 2 if ACR50 but not ACR70, 3 if ACR70
ACRuwstep	0 if not ACRuw20, 1 if ACRuw20 but not ACRuw50, 2 if ACRuw50 but not ACRuw70, 3 if ACRuw70
ACRd6wstep	0 if ACRd6w20 = 0, 1 if ACRd6w20 but not ACRd6w50, 2 if ACRd6w50 but not ACRd6w70, 3 if ACRd6w70
ACRd7wstep	0 if ACRd7w20 = 0, 1 if ACRd7w20 but not ACRd7w50, 2 if ACRd7w50 but not ACRd7w70, 3 if ACRd7w70
ACRstep3	Similar to ACRstep, but only with 20, 50 (as few achieve 70%)
ACRuwstep3	No 70%
ACRd6wstep3	No 70%
ACRd7wstep3	No 70%
Dichotomous measures of improvement	
ACR20, 30, 40, 50, 60, 70	The usual ACR20. Also tested ACR 30, 40, etc. each as dichotomous
ACRUW20, 30, 40, 50, 60, 70	ACR unweighted
ACRd6w20, 50, 70	ACR with joint counts double weighted (6 out of 9 = response)
ACRd7w20, 50, 70	ACR with joint counts double weighted (7 out of 9 = response)
MeanACR20, 30, 50	MeanACR ≥20%, 30%, 50%
SumACR-N4, 5, 6	SumACR-N ≥4, 5, 6
MedianACR20, 30, 40, 50, 60, 70	MedianACR ≥20%, 30%, 40%, 50%, 60%, 70%
MeanwACR20, 30, 40, 50, 60, 70	MeanwACR ≥20%, 30%, 40%, 50%, 60%, 70%
FifthACR20, 30, 50	FifthACR ≥20%, 30%, 50%
ThirdACR20, 30, 50	ThirdACR ≥20%, 30%, 50%
DASimp	DAS improvement (dichotomous)
LDAS1	Low disease activity based on DAS28
LDAS2	Low disease activity based on core set measurements
Hybrid definitions	
ACRhybrid	Hybrid definition: the cutoff is 20, 50, 70 based on ACR20, 50, 70; minimum (0, meanACR) if ACRstep = 0, maximum (0.2, minimum [0.5, meanACR]) if ACRstep = 1, maximum (0.5, minimum [0.7, meanACR]) if ACRstep = 2, maximum (0.7, meanACR) if ACRstep = 3
bdACRhybrid	Same as ACRhybrid but a bounded version. Replace meanACR with mean ACR_bd everywhere

* Percent change and symmetric percent change measures shown. Also tested were measures determined by absolute and not percent change (e.g., ameanACR = mean of actual changes in each core set measure).

since publication of the ACR20. Individual patient data were provided to investigators of the ACR subcommittee, with the goal of reevaluating the ACR20. Among the trials were placebo-controlled trials of disease-modifying anti-rheumatic drugs (DMARDs), different TNFα inhibitors, and a non–TNF-inhibiting biologic agent. We also obtained data from one comparative trial of a combination of agents versus a single agent. In most but not all trials, only 80% of the patient data were provided, with these patients selected at random; in the other trials, all patient data were provided. Based on agreement with sponsors providing the data, we have not provided identifiable trial information.



Core Set Item	Range	Pretreatment	Final Value	% Change
Tender Joint Count	0-68	43	14	67
Swollen Joint Count	0-66	38	4	89
Pain	0-10	4.6	2.0	56
Patient Global	0-10	8.5	3.1	63
Physician Global	0-10	7.5	2.7	64
HAQ	0-3	2.8	2.0	28
CRP (mg/dl)	>0	11.6	7.2	38

2. Did the patient improve during the trial? Yes____ No____

2a. If "Yes", was the improvement... Minimally important_____
Major improvement but NOT remission_____
Remission? _____

Figure 1. Example of a paper patient from the survey and example of the questions posed to respondents. HAQ = Health Assessment Questionnaire; CRP = C-reactive protein level.

We were prepared to exclude trials with ≥40% loss to followup, but no trial had this much loss. To analyze the data, we conducted intent-to-treat analyses using a last observation carried forward approach, preferentially selecting the 6-month outcome data when available. CRP was used as the acute-phase reactant when available, and the ESR was used if the CRP values were not available. Within each trial, we tested each candidate measure of response, focusing on the *P* value differentiating change

during active treatment versus change during placebo treatment, using Wilcoxon's rank sum test. For comparative trials, our *P* value was for the change in the combination-therapy arm versus that in the monotherapy arm. We defined this *P* value as our measure of discriminant validity.

In addition to the candidate measures of response tested, we added what we considered to be "gold standard" methods of differentiating treatments, variations on the O'Brien test, a nonparametric approach to comparing 2 groups assessed with multiple end points, which maximizes the discrimination between these groups and therefore the statistical difference between them (6). This test does not generate a response rate but compares treatments in terms of the percent improvement in each core set measure in each patient. This is not a measure that could be standardized across trials.

Step 4. Committee evaluation of data. First, an ACR subcommittee (the Committee to Reevaluate Improvement Criteria) and then the parent ACR Subcommittee on Classification and Response Criteria met to review preliminary results of the data analysis and survey. Based on advice from our statistical team, we focused on the leading 10–15 candidates, because it was likely that sensitivity to change dropped off substantially after that. Second, the parent committee and representatives of the FDA raised concerns that a joint count response was a necessary element of response definition. Thus, if they performed well, candidate measures that required or weighted the joint count response were considered preferable. Last, individual members of all committees emphasized the need to preserve the ACR20 in some manner.

RESULTS

Clinical construct validity: the survey. The survey was completed by 51 rheumatologists, mostly those attending the 2004 OMERACT (Outcome Measures in Rheumatology Clinical Trials) 7 meeting (Asilomar, CA), at which the survey was administered. Respondents included rheumatologists from the US, Canada, Australia, and several European countries. Of these, 2 had unusable data because too many responses were left blank. Examining the correlations of candidate measures of response with rheumatologists' impressions of the degree of improvement among paper patients (Table 2), we found that all correlated moderately well. The measures that performed poorly were primarily (but not exclusively) those that defined response in a dichotomous manner, such as the ACR70 or the DAS. This was because the range of improvement was not sampled by these dichotomous measures. For example, if a given patient had experienced major improvement or remission, the ACR20, a dichotomous measure, would label them only as improved and would not accurately characterize their more substantial improvement. Because of this limitation, dichotomous measures tended to have lower correlations (r values) with the range of patient improvement compared with ordinal measures, continuous measures, or measures that used an index approach to define response.

Table 2. Spearman's rank correlation coefficients (ranked from strongest to weakest) of mean survey response with candidate measure-defined response*

Variable	Spearman's correlation	*P*
%SDA1	0.96569	< 0.0001
%CDAI	0.93778	< 0.0001
n3ACRdw	0.92795	< 0.0001
n2ACRdw	0.92328	< 0.0001
%DAS	0.89903	< 0.0001
nACRdw50	0.89547	< 0.0001
n3ACR	0.87737	< 0.0001
n2ACR	0.86971	< 0.0001
nACR50	0.86144	< 0.0001
nACRdw	0.84058	< 0.0001
ACR-N	0.83657	< 0.0001
ACRhybrid	0.83150	< 0.0001
bdACRhybrid	0.82231	< 0.0001
%ODAI	0.80802	< 0.0001
ACRstep	0.79135	< 0.0001
nACR	0.78574	< 0.0001
MedianACR	0.77829	< 0.0001
n3ACRw	0.77121	< 0.0001
ACRuw50	0.76574	< 0.0001
FifthACR50	0.76574	< 0.0001
ACRstep3	0.76277	< 0.0001
nACRw	0.75884	< 0.0001
n2ACRw	0.75826	< 0.0001
ACR30	0.74588	< 0.0001
ACR20	0.73140	< 0.0001
ACR40	0.71090	< 0.0001
LDAS1	0.68017	< 0.0001
EULAR	0.66271	< 0.0001
nACRw50	0.65902	< 0.0001
MeanwACR50	0.64574	< 0.0001
ACRuw30	0.62228	< 0.0001
FifthACR30	0.62228	< 0.0001
ACR50	0.60604	< 0.0001
ThirdACR50	0.58918	< 0.0001
ACRuw20	0.58586	0.0001
FifthACR20	0.58586	0.0001
ACR70	0.57165	0.0002
MeanACR	0.55360	0.0003
MeanACR_bd	0.55338	0.0003
MeanACR30	0.50842	0.0011
LDAS2	0.48516	0.0020
MeanACR20	0.46735	0.0031
MeanwACR30	0.46149	0.0035
MeanwACR70	0.45426	0.0042
MedianACR20	0.43411	0.0065
DASimp	0.35198	0.0302

* For definitions, see Table 1.

Discriminant validity: trial data. We turned to analysis of RA trial data, displaying candidates in order of the most sensitive to change to the least sensitive to change (Table 3). For each candidate measure, we produced an average rank of its sensitivity to change compared with all other candidate measures (average rank) and a weighted average rank that weights each trial by its study size. The minimum/maximum rankings range from 1 to 135, because we tested a total of 135 candidate measures, although (because of space limitations) we show only measures of interest. The measure with the greatest sensitivity to change was a

data-driven measure designed to be our gold standard, based on the O'Brien test.

The top scoring measures were those that counted the number of core set measures that improved by 20%, 50%, and 70%. This group of measures includes the n3ACR and the n3ACRdw (doubly weighted for joint count). The n3ACR definitions characterize a patient as having improved by 20%, 50%, or 70% in each of the core set measures, in which they would get, respectively, a score of 1, 2, or 3 for that core set measure. The n3ACR count for a given patient would range from 0 to 21, with a score of 21 being achieved if the patient had at least 70% improvement in all core set measures.

Next in the ranking of candidate measures was the hybrid measure, the bdACRhybrid. This measure combined the ACR20, ACR50, and ACR70 scores with a patient's mean improvement in core set measures. Because the patient in Figure 1 from the survey met the ACR50 criteria but not the ACR70 criteria, that patient had a bdACRhybrid score between 50 and 70. The patient's mean percent improvement in core set measures was 57.9, which is the bdACRhybrid score. The scores for other patients are presented in Appendix A.

The bdACRhybrid variable is limited to an overall score of −100 to +100. Given that when core set measures improve there is a drop in score, these measures cannot improve more than 100%, thereby setting an upper bound. This particular hybrid measure was also limited to −100 (maximal worsening). We tested unbounded versions of the hybrid, in which the score was allowed to decrease according to the mean percent worsening, but these hybrid versions were not as sensitive to change as the bounded version, perhaps because they permitted outlier values to have a greater effect.

When we examined other candidate measures of response, we found that their discriminant validity was less than that of the above-described measures (Table 3). These included commonly recommended measures, such as the EULAR criteria for improvement and the ACR-N. Dichotomous measures of improvement, such as the ACR20, were farther down the list, and the worst scoring measure tested was one of the measures of low disease activity. Both measures of low disease activity scored poorly, suggesting that low disease activity should not be used as a primary outcome measure in trials.

The difference between the best and the worst candidate scoring measures was substantial. For example, in a trial of conventional DMARDs, the worst scoring measures showed no significant difference between the efficacy of second-line drug and placebo, whereas the top scoring measures showed a significant difference between drug and placebo ($P < 0.001$). In general, the difference between the worst and the best groups of measures in terms of P values ranged from 10^{-3} to 10^{-6}, which represents a huge difference between the ability of the most and the least sensitive candidate measures to detect differences between therapies. Thus, the efficacy of some drugs versus placebo (or modest efficacy differences between 2 treatments) would not be detected if candidate measures at the bottom of the list were used. Our results also translate to smaller sample sizes needed in trials to detect the same treatment effects with statistical significance. For example, to achieve 80% power with a significance level of 0.05, a trial using the ACR20 would need 200 patients in order to detect a specific difference in treatments. Using the hybrid ACR response measure, only 108 patients would be needed to detect the same difference with the same power.

The committee considered data on the sensitivity to change of different candidate measures. Initially, because dichotomous measures had worse construct validity than did ordinal or continuous measures and were consistently among the worst performing candidate measures of response, these were rejected in our deliberations. We focused instead on the 10–15 measures that performed best. Additional concerns that were considered were understandability of the candidate measure, its compatibility with the ACR20, and its emphasis on joint count improvement without compromising sensitivity to change.

The options considered by the ACR committee and its parent committee included variations on the n3ACR and the bdACRhybrid. Because the other measures had worse sensitivity to change and did not preserve the ACR20/50/70 approach and/or they were not understandable, they were eliminated from consideration. Ultimately, the Committee to Reevaluate Improvement Criteria, working with the parent committee, selected the bdACRhybrid (which we will call the "hybrid ACR response measure") for the following reasons:

1. It was highly sensitive to change (ranked close to the top of all measures tested).
2. It incorporated a requirement for joint count improvement without compromising sensitivity to change.
3. It preserved the ACR20/50/70; the proportion of patients improving by these amounts is easily determined from data in which the bdACRhybrid is used.
4. It could be understood readily.

Scoring of the hybrid ACR response measure is shown in Table 4.

DISCUSSION

Using a data-driven consensus approach, a committee constituted by the ACR has revised the ACR definition of response and recommended a new hybrid measure that incorporates a patient-specific definition of improvement, allowing for the computation of ACR 20%, 50%, and 70% improvements, yet also incorporating a continuous measure of change. This measure addresses conflicting needs in defining improvement; that is, developing a measure that optimally detects modest differences between therapies, and retaining a standard measure that does not discard the widely used ACR20.

The hybrid ACR response measure is intended for use as an outcome measure in clinical trials. Its use enables modest treatment differences to be detected as statistically significant and allows trials to be carried out with fewer subjects than are required using current outcome measures.

Because drug developers may rely on this measure to perform smaller pivotal trials than are currently undertaken to gain FDA approval, use of the hybrid ACR re-

Table 3. Ranking of the discriminant validity among 135 candidate definitions in rheumatoid arthritis trials*

Candidate definition	Rank of definition among all tested using weighted average of trial data	Lowest (best) rank for candidate among all trials	Highest (worst) rank for candidate among all trials
O'Brien%†	1	1	27
n3ACR†	3	1	52
n3ACRdw	4	2	50
bdACRhybrid†	7	1	50
MeanACR_bd†	8	1	54
n2ACR	9	4	61
n2ACRdw	10	5	58
MeanACR2	15	6	60
ACRhybrid†	18	2	49
%DAS†	20	1.5	89.5
%SDAI†	27	1	122
MeanACR	28	5	85
MedianACR	31	5	89
nACR†	32	3	80
nACRdw	33	1	78
nACR50	34	4	66
nACRdw50	35	6	73
%CDAI	45	21	86
%ODAI	46	20	70
MedianACR2	49	20	79
n3ACRw	50	8	105
ACR-N†	53	14	93
EULAR†	54	7	111
n2ACRw	55	12	102
nACRw	62	7	98
ACRstep (ACR20,50,70)	64	12	97
ThirdACR30	69	1	131
MedianACR30	70	17	130
ACRstep3	72	51	103
DASimp†	74	5	126
ThirdACR50	77	36	113
ACRuw30	78	13.5	111.5
FifthACR30	79	13.5	111.5
MeanwACR30	83	5	116
ACRuw20	87	7	131
FifthACR20	88	7	131
MeanACR20	90	22	122
MeanACR30	91	11	129
MedianACR20	92	39.5	125.5
nACRw50	96	31	129
MeanwACR50	97	41	129
ACR20†	101	40	122
LDAS1	107	18	131
ACR30	110	76	118
ThirdACR20	113	11	130
ACR40	116	84	128
ACRuw50	118	61	118
FifthACR50	119	61	118
ACR50†	123	68	133
ACR70†	130	18	133
LDAS2	135	82	133

* Most widely clinically used measures and other representative results are presented. For definitions, see Table 1.
† Candidates of special interest.

sponse measure may make safety data less complete at the time of drug approval.

Disease activity states and response measures are not the same, and the former may be useful in clinical practice and even as a measure of the attained state in trials (e.g., low disease activity, remission). Our effort does not supplant

Table 4. Scoring method for the Hybrid American College of Rheumatology (ACR) response measure*

ACR status	Mean % change in core set measures			
	<20	≥20, <50	≥50, <70	≥70
Not ACR20	Mean % change	19.99	19.99	19.99
ACR20 but not ACR50	20	Mean % change	49.99	49.99
ACR50 but not ACR70	50	50	Mean % change	69.99
ACR70	70	70	70	Mean % change

* 1) Calculate the average percentage change in core set measures. For each core set measure, subtract score after treatment from baseline score and determine percentage improvement in each measure. Next, if a core set measure worsened by >100%, limit that percentage change to 100% (a − 100% bound). Then average the percentage changes for all core set measures. 2) Determine whether the patient has achieved: ACR20, ACR50, or ACR70. 3) Using the table above, obtain the Hybrid ACR response measure. To use the table, take the ACR20, ACR50, or ACR70 status of the patient (left column) and the mean percentage improvement in core set items; the Hybrid ACR score is where they intersect in the table.

valuable efforts by other groups of investigators to define different states of activity in RA, including low disease activity and remission. We do, however, suggest that the current definitions of low disease activity (and, by extension, remission) should not be used as primary outcome measures in trials, because they are among the least sensitive to change of the measures we evaluated. Our data also suggest that the available disease activity state measures do not perform as well in trials as does the new hybrid ACR response measure.

Our approach has some important limitations. First, we made several critical assumptions that affected our choice. We accepted the validity and high performance of the core set of outcome measures. Other core set measures might yield a different definition of response. Second, although our list of candidate measures was large, we may not have considered certain approaches that might have altered our decisions. Third, even with the assumptions, we may have produced a different answer using a different set of trial data, although our trials were large and varied enough that we suspect the ranking of candidate measures would not have changed much. Fourth, our candidate measures may rank slightly different if a different analytic approach (e.g., parametric analysis) were used, although in such an approach, outliers would be likely to compromise power to a greater extent.

Although requiring improvement in both the tender joint count and especially the swollen joint count can compromise the sensitivity to change of outcome measurement in RA, we believe there are creative solutions to this problem. We have proposed one solution, the hybrid ACR response measure, which requires improvement in the swollen and tender joint counts to reach a certain threshold score. Combined with the mean percent improvement in core set measures, one can derive the ACR hybrid measure score (see Table 4). To make it clear how this works, we provide additional tables in which we compute the new recommended response measure (see Appendix A).

We noted earlier that one major source of measurement heterogeneity in RA trials has been the varied ways in which the ACR20 has been defined. There are a variety of ways in which the hybrid ACR measure could be used based on timing of measurement. In another report, we shall propose an approach to timing of the hybrid ACR measure in trials so as to encourage more uniformity in measuring response in RA trials.

In summary, we suggest a revision to the ACR20 that creates a new hybrid outcome measure, a measure combining the ACR20, the ACR50, and the ACR70 and a continuous score of the mean improvement in core set measures. This new measure has much greater statistical power to distinguish the efficacy of treatments than do the currently recommended measures of response, including the ACR20.

AUTHOR CONTRIBUTIONS

Dr. Felson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Felson, Xie, LaValley, Anderson, Furst, Boers, Pincus, Dougados, Bombardier, Simon.

Acquisition of data. Felson, Xie, Anderson, Wolfe, Furst, White.

Analysis and interpretation of data. Felson, Xie, LaValley, Anderson, Koch, Wolfe, Michaud, Furst, Boers, Bathon, Tugwell, Pincus, Dougados, van der Heijde, Smolen, Aletaha, Siegel, Choi, Paulus, White, Landewé, Simon.

Manuscript preparation. Felson, Xie, LaValley, Koch, Michaud, Furst, Boers, Smolen, Aletaha, Siegel, Choi, Paulus, Bombardier, Landewé.

Statistical analysis. Felson, Xie, LaValley, Koch, Furst.

Background indices. Pincus.

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APPENDIX A. AMERICAN COLLEGE OF RHEUMATOLOGY HYBRID SCORE OF 3 TRIAL PATIENTS

Patient 1. The patient did not meet the criteria for ACR20 (swollen joint count worsened). Therefore, the Hybrid ACR score must be <20, even though the mean change of all scores is 42.8. The Hybrid ACR score for this patient is 19.99.

Core set item	Range	Pretreatment	Final value	% change
Tender joint count	0–68	43	14	67
Swollen joint count	0–66	38	44	−16*
Pain	0–10	4.6	2.0	56
Patient global	0–10	8.5	3.1	63
Physician global	0–10	7.5	2.7	64
Health Assessment Questionnaire	0–3	2.8	2.0	28
C-reactive protein level (mg/dl)	>0	11.6	7.2	38

* Swollen joint count has worsened.

Patient 2. The patient met the criteria for ACR50 but not ACR70. Therefore, the Hybrid ACR score must be between 50 and 69.99. The mean percentage improvement is 73.29%. The ACR Hybrid score (limited by the failure of the patient to reach ACR70) is 69.99.

Core set item	Range	Pretreatment	Final value	% change
Tender joint count	0–68	43	14	67
Swollen joint count	0–66	38	14	63
Pain	0–10	4.6	1.0	78
Patient global	0–10	8.5	1.1	87
Physician global	0–10	7.5	2.7	64
Health Assessment Questionnaire	0–3	2.8	1.0	64
C-reactive protein level (mg/dl)	>0	11.6	1.2	90

Patient 3. The patient met the criteria for ACR50 but not ACR70. Therefore, the Hybrid ACR score must be between 50 and 69.99. The mean percentage change is 52.29, and the ACR Hybrid score is 52.29.

Core set item	Range	Pretreatment	Final value	% change
Tender joint count	0–68	43	14	67
Swollen joint count	0–66	38	19	50
Pain	0–10	4.6	2.0	56
Patient global	0–10	8.5	3.1	63
Physician global	0–10	7.5	2.7	64
Health Assessment Questionnaire	0–3	2.8	2.0	28
C-reactive protein level (mg/dl)	>0	11.6	7.2	38

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American College of Rheumatology (ACR) Guideline for the Screening, Monitoring, and Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease

Project Plan – August 2022

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American College of Rheumatology (ACR) Guideline for the Screening, Monitoring, and Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease

Project Plan – August 2022

ORGANIZATIONAL LEADERSHIP AND SUPPORT

This project is led and funded by the American College of Rheumatology (ACR).

BACKGROUND

Interstitial lung disease (ILD), a heterogeneous group of disorders characterized by inflammation and fibrosis of the lung parenchyma, is a significant cause of morbidity and mortality in people with systemic autoimmune rheumatic diseases (ARDs). Although all people with ARDs are at risk for developing ILD, those with systemic sclerosis (SSc), rheumatoid arthritis (RA), mixed connective tissue disease (MCTD), polymyositis/dermatomyositis (PM/DM), and Sjogren's Syndrome (SS) are at the greatest risk (1,2) For example, ILD affects approximately 40-60% of adults with SSc and is the leading cause of death and hospitalization in this population (3-6).

Despite the life-threatening nature of ARD-ILD and the emerging potential of new therapies to arrest disease progression, there are no clinical practice guidelines for ILD screening or treatment in the ARDs. It is hypothesized that screening for ARD-ILD could lead to early interventions to prevent or slow progression of this often lethal disease. Hence, there is an urgent need to develop ARD-ILD screening, monitoring, and treatment guidelines.

OBJECTIVES

The objective of this project is to develop a clinical practice guideline that includes evidence-based consensus recommendations for clinicians who care for people with systemic autoimmune rheumatic disease who are at risk for or have been diagnosed with interstitial lung disease (ILD).

Specifically, we aim to:

1. Develop recommendations regarding optimal screening tests to screen for ILD in people with specific ARDs.
2. Develop recommendations for the monitoring of ARD-ILD (monitoring for both the development and progression of ARD-ILD).
3. Develop treatment recommendations for ARD-ILD.

THEMES OF PICO QUESTIONS

The PICO (Population/patients, Intervention, Comparator, and Outcomes; *see Appendix A*) questions developed for this guideline fall into 5 major categories:

American College of Rheumatology (ACR) Guideline for the Screening, Monitoring, and Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease

Project Plan – August 2022

1. Screening for ILD in people with rheumatic disease at increased risk of developing ILD
2. Monitoring ILD progression and treatment complications
3. Treatment of ILD: first therapy
4. Treatment of ILD after ILD progression on first ILD therapy
5. Treatment of rapidly progressive ILD

METHODS

Identification of Studies

Literature search strategies, based on PICO questions, were drafted by a research librarian with input from the Core Team. Searches were performed in OVID Medline (1946 +), Embase (1974 +), and PubMed (mid-1960s +).

The search strategies were developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for OVID Medline and PubMed; and Emtree terms for Embase. Text words were also used in OVID Medline, PubMed, and Embase.

Search Limits

Only English language articles will be retrieved.

Literature Search Update

Literature searches will be updated just before the voting panel meeting to ensure completeness.

Inclusion/Exclusion Criteria

Appendix A includes the project's PICO questions, which outline the defined patient population, interventions, comparators, and outcomes. *Appendix B* includes the list of inclusion/exclusion criteria.

Management of Studies and Data

References and abstracts will be imported into bibliographic management software (EndNote) (7), duplicates removed, and exported to Distiller SR, a web-based systematic review manager (8). Screening and data abstraction forms will be created in Distiller SR. Search results will be divided among reviewers, and two reviewers will screen each title/abstract, with disagreements at the title/abstract screening stage defaulting to inclusion for full manuscript review. Following the same dual review process, disagreements at the full manuscript screening stage will be discussed and adjudicated by the literature review leadership, if necessary.

Phases

1. A search for randomized controlled trials and observational studies will be performed to determine existing studies covering outcomes of interest.

2. Additionally, recently published systematic reviews covering outcomes of interest will also be sought and used for reference cross-checking.
3. Chosen studies will be quality-assessed using the Instrument to assess the Credibility of Effect Modification Analyses.
4. Subsequently, identified studies will be assessed using the RevMan (10) and GRADE Pro tools (11).

GRADE Methodology

GRADE methodology will be used in this project to grade available evidence and facilitate development of recommendations. The certainty in the evidence (also known as 'quality' of evidence) will be graded as high, moderate, low or very low. The recommendations will have a strength, strong or conditional, and a direction, as in favor of or against the intervention. The strength of recommendations will not depend solely on the certainty in the evidence, but also on patient preferences and values, and the weight between benefits and harms. A series of articles that describe the GRADE methodology can be found on the GRADE working group's website: www.gradeworkinggroup.org.

Data Analysis and Synthesis

The literature review team will analyze and synthesize data from included studies that address the PICO questions. An evidence profile, including a GRADE Summary of Findings table, will be prepared for each PICO question using Review Manager (RevMan) (10) and GRADEprofiler (GRADEpro) software (11). The Summary of Findings table contains the benefits and harms for each outcome across studies, the assumed and corresponding risk for comparators and interventions (95% CI), the absolute risk and relative effect (95% CI), the number of participants/number of studies, and the certainty in the evidence for each critical and important outcome (i.e., high, moderate, low or very low).

The evidence profile documents the overall certainty in the evidence for each critical and important outcome across studies and summarizes the rationale of the GRADE criteria for downgrading (risk of bias, inconsistency, indirectness, imprecision, and publication bias), or upgrading the certainty in a body of evidence (large magnitude of effect, dose-response gradient, and all plausible confounding that would reduce a demonstrated effect).

Development of Recommendation Statements

PICO questions will be revised into drafted recommendation statements. Using the GRADE Evidence Profiles and Summaries of Findings tables, the voting panel, consisting of 11 rheumatologists, 5 pulmonologists, 1 radiologist, and at least 2 patients with rheumatic disease-associated ILD (specifically, ILD associated with either systemic sclerosis, rheumatoid arthritis, mixed connective tissue disease, dermatomyositis, polymyositis, or Sjogren's syndrome), will consider the drafted recommendation statements in two stages. The first assessment will be done individually, and the results will be

anonymous; this vote will only be used to determine where consensus might or might not already exist and develop an agenda for a virtual voting panel meeting. At the virtual voting panel meeting, chaired by the principal investigators, the panelists will discuss the evidence in the context of their clinical experience and expertise to arrive at consensus on the final recommendations. The voting panel meeting discussions will be supported by the GRADE expert as well as the literature review leader, who will attend the meeting to provide details about the evidence, as requested. Voting panel discussions and decisions will also be informed by a separately convened patient panel, which will meet in the days before the voting panel meeting, to provide unique patient perspectives on the drafted recommendations based on their experiences and the available literature.

PLANNED APPENDICES (AT MINIMUM)

A. Final literature search strategies
B. Inclusion/exclusion criteria
C. GRADE evidence profiles and summary of findings tables for each PICO question

AUTHORSHIP

Authorship of the guideline will include co-principal investigators Sindhu R. Johnson, MD, PhD, and Elana J. Bernstein, MD, MSc; co-literature review leaders Ilya Ivlev, MD, PhD, MBI and Stacey Uhl; MS content experts Marcy B. Bolster, MD, Jonathan H. Chung, MD, Sonye Danoff, MD, PhD, Michael George, MD, MSCE, and Dinesh Khanna, MD; and Gordon Guyatt, MD, GRADE expert, and Reza Mirza, MD, GRADE/Methodological Contributor. Members of the voting panel and literature review team will also be authors. The PIs will determine final authorship, dependent on the efforts made by individuals throughout the guideline development process, using international authorship standards as guidance.

DISCLOSURES/CONFLICTS OF INTEREST

The ACR's disclosure and COI policies for guideline development will be followed for this project. These can be found in the ACR Guideline Manual on this page of the ACR web site, under Policies & Procedures. *See Appendix D for participant disclosures.*

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American College of Rheumatology (ACR) Guideline for the Screening, Monitoring, and Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease

Project Plan – August 2022

ARDs included in this project

1. **Systemic sclerosis**
2. **Rheumatoid arthritis**
3. **Inflammatory myopathy**
4. **Sjogren's Syndrome**
5. **Mixed connective tissue disease**

SUMMARY OF PICO QUESTIONS

Screening PICO questions:

In people with ARD at increased risk of developing ILD, what is the impact of each of the following tests on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- PFTs vs. history/physical
- High resolution CT thorax vs. history/physical
- 6-minute walk test distance vs. history/physical
- Chest radiograph vs. history/physical
- Ambulatory desaturation vs. history/physical
- Chest radiograph vs. high resolution CT thorax
- PFTs vs. ambulatory desaturation
- High resolution CT thorax vs. PFTs
- High resolution CT thorax and PFTs vs. PFTs alone
- Bronchoscopy vs. no bronchoscopy
- Surgical lung biopsy vs. no surgical lung biopsy

Monitoring PICO questions:

In people with ARD who also have ILD, what is the impact of each of the following tests on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

- PFTs vs. history/physical
- High resolution CT thorax vs. history/physical
- 6-minute walk test distance vs. history/physical
- Chest radiograph vs. history/physical
- Ambulatory desaturation vs. history/physical
- Chest radiograph vs. high resolution CT thorax
- Bronchoscopy vs. no bronchoscopy

- High resolution CT thorax vs. bronchoscopy
- PFTs vs. 6-minute walk test distance
- PFTs and 6-minute walk test distance vs. PFTs alone
- PFTs vs. ambulatory desaturation
- PFTs and high resolution CT thorax vs. PFTs alone
- 6-minute walk test distance vs. ambulatory desaturation

Medical management – 1st ILD therapy PICO questions:

In people with ARD who also have ILD, what is the impact of each of the following therapies as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

- Mycophenolate vs. no mycophenolate
- Cyclophosphamide vs. no cyclophosphamide (I/V or oral)
- Leflunomide vs. no leflunomide
- Methotrexate vs. no methotrexate
- Azathioprine vs. no azathioprine
- Calcineurin inhibitors vs. no calcineurin inhibitors
- Anti-TNF therapy vs. no anti-TNF therapy
- Abatacept vs. no abatacept
- Anti-CD20 antibody vs. no anti-CD20 antibody
- IL-6 receptor antagonists vs. no IL-6 receptor antagonists
- JAK inhibitors vs. no JAK inhibitors
- Daily oral prednisone vs. no daily oral prednisone
- IV pulse glucocorticoids vs. no IV pulse glucocorticoids
- Nintedanib vs. no nintedanib
- Pirfenidone vs. no pirfenidone
- IVIG vs. no IVIG
- Plasma exchange vs. no plasma exchange
- Adding nintedanib to mycophenolate vs. not adding nintedanib to mycophenolate
- Adding pirfenidone to mycophenolate vs. not adding pirfenidone to mycophenolate
- Upfront combination of nintedanib with mycophenolate vs. mycophenolate alone
- Upfront combination of pirfenidone with mycophenolate vs. mycophenolate alone
- Methotrexate vs. mycophenolate
- Leflunomide vs. mycophenolate
- Azathioprine vs. mycophenolate
- I/V or oral cyclophosphamide vs. mycophenolate
- Calcineurin inhibitors vs. mycophenolate

- TNF inhibitors vs. mycophenolate
- IL-6 receptor antagonists vs. mycophenolate
- Anti-CD20 antibody vs. mycophenolate
- Abatacept vs. mycophenolate
- JAK inhibitors vs. mycophenolate
- Nintedanib vs. mycophenolate
- Pirfenidone vs. mycophenolate
- IVIG vs. mycophenolate
- Oral prednisone vs. mycophenolate
- Intravenous methylprednisolone vs. mycophenolate
- Plasma exchange vs. mycophenolate
- Methotrexate vs. anti-CD20 antibody
- Leflunomide vs. anti-CD20 antibody
- Azathioprine vs. anti-CD20 antibody
- I/V or oral cyclophosphamide vs. anti-CD20 antibody
- Calcineurin inhibitors vs. anti-CD20 antibody
- TNF inhibitors vs. anti-CD20 antibody
- IL-6 receptor antagonists vs. anti-CD20 antibody
- Abatacept vs. anti-CD20 antibody
- JAK inhibitors vs. anti-CD20 antibody
- Nintedinib vs. anti-CD20 antibody
- Pirfenidone vs. anti-CD20 antibody
- IVIG vs. anti-CD20 antibody
- Oral prednisone vs. anti-CD20 antibody
- Intravenous methylprednisolone vs. anti-CD20 antibody
- Plasma exchange vs. anti-CD20 antibody
- Methotrexate vs. azathioprine
- Leflunomide vs. azathioprine
- I/V or oral cyclophosphamide vs. azathioprine
- Calcineurin inhibitors vs. azathioprine
- TNF inhibitors vs. azathioprine
- IL-6 receptor antagonists vs. azathioprine
  Abatacept vs. azathioprine
- JAK inhibitors vs. azathioprine
- Nintedinib vs. azathioprine

- Pirfenidone vs. azathioprine
- IVIG vs. azathioprine
- Oral prednisone vs. azathioprine
- Intravenous methylprednisolone vs. azathioprine
- Plasma exchange vs. azathioprine
- Methotrexate vs. I/V or oral cyclophosphamide
- Leflunomide vs. I/V or oral cyclophosphamide
- Calcineurin inhibitors vs. I/V or oral cyclophosphamide
- TNF inhibitors vs. I/V or oral cyclophosphamide
- IL-6 receptor antagonists vs. I/V or oral cyclophosphamide
- Abatacept vs. I/V or oral cyclophosphamide
- JAK inhibitors vs. I/V or oral cyclophosphamide
- Nintedinib vs. I/V or oral cyclophosphamide
- Pirfenidone vs. I/V or oral cyclophosphamide
- IVIG vs. I/V or oral cyclophosphamide
- Oral prednisone vs. I/V or oral cyclophosphamide
- Intravenous methylprednisolone vs. I/V or oral cyclophosphamide
- Plasma exchange vs. I/V or oral cyclophosphamide
- Nintedanib vs. IL-6 receptor antagonists
- Referral for stem cell transplant vs. optimal medical management
- Referral for lung transplant vs. optimal medical management

Medical management – ILD progression on any 1st ILD therapy PICO questions

In ARD patients with ILD progression after 1st ILD therapy, what is the impact of adding each of the following therapies on disease-related outcomes and treatment-related adverse events?

- Combination of nintedanib and mycophenolate vs. mycophenolate alone
- Combination of pirfenidone and mycophenolate vs. mycophenolate alone
- Methotrexate vs. mycophenolate
- Leflunomide vs. mycophenolate
- Azathioprine vs. mycophenolate
- I/V or oral cyclophosphamide vs. mycophenolate
- Calcineurin inhibitors vs. mycophenolate
- TNF inhibitors vs. mycophenolate
- IL-6 receptor antagonists vs. mycophenolate
- Anti-CD20 antibody vs. mycophenolate
- Abatacept vs. mycophenolate

- JAK inhibitors vs. mycophenolate
- Nintedinib vs. mycophenolate
- Pirfenidone vs. mycophenolate
- IVIG vs. mycophenolate
- Oral prednisone vs. mycophenolate
- Intravenous methylprednisolone vs. mycophenolate
- Plasma exchange vs. mycophenolate
- Methotrexate vs. anti-CD20 antibody
- Leflunomide vs. anti-CD20 antibody
- Azathioprine vs. anti-CD20 antibody
- I/V or oral cyclophosphamide vs. anti-CD20 antibody
- Calcineurin inhibitors vs. anti-CD20 antibody
- TNF inhibitors vs. anti-CD20 antibody
- IL-6 receptor antagonists vs. anti-CD20 antibody
- Abatacept vs. anti-CD20 antibody
- JAK inhibitors vs. anti-CD20 antibody
- Nintedinib vs. anti-CD20 antibody
- Pirfenidone vs. anti-CD20 antibody
- IVIG vs. anti-CD20 antibody
- Oral prednisone vs. anti-CD20 antibody
- Intravenous methylprednisolone vs. anti-CD20 antibody
- Plasma exchange vs. anti-CD20 antibody
- Methotrexate vs. azathioprine
- Leflunomide vs. azathioprine
- I/V or oral cyclophosphamide vs. azathioprine
- Calcineurin inhibitors vs. azathioprine
- TNF inhibitors vs. azathioprine
- IL-6 receptor antagonists vs. azathioprine
- Abatacept vs. azathioprine
- JAK inhibitors vs. azathioprine
- Nintedinib vs. azathioprine
- Pirfenidone vs. azathioprine
- IVIG vs. azathioprine
- Oral prednisone vs. azathioprine
- Intravenous methylprednisolone vs. azathioprine

- Plasma exchange vs. azathioprine
- Methotrexate vs. I/V or oral cyclophosphamide
- Leflunomide vs. I/V or oral cyclophosphamide
- Calcineurin inhibitors vs. I/V or oral cyclophosphamide
- TNF inhibitors vs. I/V or oral cyclophosphamide
- IL-6 receptor antagonists vs. I/V or oral cyclophosphamide
- Abatacept vs. I/V or oral cyclophosphamide
- JAK inhibitors vs. I/V or oral cyclophosphamide
- Nintedinib vs. I/V or oral cyclophosphamide
- Pirfenidone vs. I/V or oral cyclophosphamide
- IVIG vs. I/V or oral cyclophosphamide
- Oral prednisone vs. I/V or oral cyclophosphamide
- Intravenous methylprednisolone vs. I/V or oral cyclophosphamide
- Plasma exchange vs. I/V or oral cyclophosphamide
- Referral for stem cell transplant vs. optimal medical management
- Referral for lung transplant vs. optimal medical management

Medical management – rapidly progressive ILD PICO questions

In ARD patients with rapidly progressive ILD, what is the impact of each of the following therapies as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

- Daily oral prednisone vs. no daily oral prednisone
- Pulse intravenous glucocorticoids vs. no pulse intravenous glucocorticoids
- Nintedanib vs. no nintedanib
- Pirfenidone vs. no pirfenidone
- Adding nintedanib to mycophenolate vs. not adding nintedanib to mycophenolate
- Adding pirfenidone to mycophenolate vs. not adding pirfenidone to mycophenolate
- Upfront combination of nintedanib with mycophenolate vs. mycophenolate alone
- Upfront combination of pirfenidone with mycophenolate vs. mycophenolate alone
- Methotrexate vs. mycophenolate
- Leflunomide vs. mycophenolate
- Azathioprine vs. mycophenolate
- I/V or oral cyclophosphamide vs. mycophenolate
- Calcineurin inhibitors vs. mycophenolate
- TNF inhibitors vs. mycophenolate
- IL-6 receptor antagonists vs. mycophenolate
- Anti-CD20 antibody vs. mycophenolate

- Abatacept vs. mycophenolate
- JAK inhibitors vs. mycophenolate
- Nintedinib vs. mycophenolate
- Pirfenidone vs. mycophenolate
- IVIG vs. mycophenolate
- Oral prednisone vs. mycophenolate
- Intravenous methylprednisolone vs. mycophenolate
- Plasma exchange vs. mycophenolate
- Methotrexate vs. anti-CD20 antibody
- Leflunomide vs. anti-CD20 antibody
- Azathioprine vs. anti-CD20 antibody
- I/V or oral cyclophosphamide vs. anti-CD20 antibody
- Calcineurin inhibitors vs. anti-CD20 antibody
- TNF inhibitors vs. anti-CD20 antibody
- IL-6 receptor antagonists vs. anti-CD20 antibody
- Abatacept vs. anti-CD20 antibody
- JAK inhibitors vs. anti-CD20 antibody
- Nintedinib vs. anti-CD20 antibody
- Pirfenidone vs. anti-CD20 antibody
- IVIG vs. anti-CD20 antibody
- Oral prednisone vs. anti-CD20 antibody
- Intravenous methylprednisolone vs. anti-CD20 antibody
- Plasma exchange vs. anti-CD20 antibody
- Methotrexate vs. azathioprine
- Leflunomide vs. azathioprine
- I/V or oral cyclophosphamide vs. azathioprine
- Calcineurin inhibitors vs. azathioprine
- TNF inhibitors vs. azathioprine
- IL-6 receptor antagonists vs. azathioprine
- Abatacept vs. azathioprine
- JAK inhibitors vs. azathioprine
- Nintedinib vs. azathioprine
- Pirfenidone vs. azathioprine
- IVIG vs. azathioprine
- Oral prednisone vs. azathioprine

- Intravenous methylprednisolone vs. azathioprine
- Plasma exchange vs. azathioprine
- Methotrexate vs. cyclophosphamide
- Leflunomide vs. cyclophosphamide
- Calcineurin inhibitors vs. I/V or oral cyclophosphamide
- TNF inhibitors vs. I/V or oral cyclophosphamide
- of IL-6 receptor antagonists vs. I/V or oral cyclophosphamide
- Abatacept vs. I/V or oral cyclophosphamide
- JAK inhibitors vs. I/V or oral cyclophosphamide
- Nintedinib vs. I/V or oral cyclophosphamide
- Pirfenidone vs. I/V or oral cyclophosphamide
- IVIG vs. I/V or oral cyclophosphamide
- Oral prednisone vs. I/V or oral cyclophosphamide
- Intravenous methylprednisolone vs. I/V or oral cyclophosphamide
- Plasma exchange vs. I/V or oral cyclophosphamide
- Dual combination therapy* vs. monotherapy†
- Triple combination therapy‡ vs. monotherapy†
- Triple combination therapy‡ vs. dual combination therapy*
- IVIG and/or plasma exchange in addition to monotherapy†, dual combination therapy*, or triple combination therapy‡ vs. monotherapy†, dual combination therapy*, or triple combination therapy‡ alone
- Antifibrotic (e.g., nintedanib or pirfenidone) in addition to monotherapy†, dual combination therapy*, or triple combination therapy‡ vs. monotherapy†, dual combination therapy*, or triple combination therapy‡ alone
- Referral for stem cell transplant vs. optimal medical management
- Referral for lung transplant vs. optimal medical management

APPENDIX A – PICO Questions

Screening for ILD in people with rheumatic disease at increased risk of developing ILD

1. In people with rheumatic disease at increased risk of developing ILD, what is the impact of pulmonary function tests (PFTs) compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

2. In people with rheumatic disease at increased risk of developing ILD, what is the impact of high resolution CT thorax compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

3. In people with rheumatic disease at increased risk of developing ILD, what is the impact of 6-minute walk test distance compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

4. In people with rheumatic disease at increased risk of developing ILD, what is the impact chest radiograph compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

5. In people with rheumatic disease at increased risk of developing ILD, what is the impact of ambulatory desaturation compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

6. In people with rheumatic disease at increased risk of developing ILD, what is the impact of chest radiograph compared to high resolution CT thorax on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

7. In people with rheumatic disease at increased risk of developing ILD, what is the impact of pulmonary function tests (PFTs) compared to ambulatory desaturation on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

8. In people with rheumatic disease at increased risk of developing ILD, what is the impact of high resolution CT thorax compared to PFTs on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

9. In people with rheumatic disease at increased risk of developing ILD, what is the impact of high resolution CT thorax and PFTs compared to PFTs alone on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

10. In people with rheumatic disease at increased risk of developing ILD, what is the impact of bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy) compared to no bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy) on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

11. In people with rheumatic disease at increased risk of developing ILD, what is the impact of surgical lung biopsy compared to no surgical lung biopsy on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

Monitoring disease progression and treatment complications

12. In people with rheumatic disease with ILD, what is the impact of pulmonary function tests (PFTs) compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

13. In people with rheumatic disease with ILD, what is the impact of high resolution CT thorax compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

14. In people with rheumatic disease with ILD, what is the impact of 6-minute walk test distance compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination: crackles on auscultation) on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

15. In people with rheumatic disease with ILD, what is the impact of chest radiograph compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physical examination:

crackles on auscultation) on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

16. In people with rheumatic disease with ILD, what is the impact ambulatory desaturation compared to history/physical alone (e.g., shortness of breath (dyspnea), functional class and physician examination: crackles on auscultation) on responsiveness/sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

17. In people with rheumatic disease with ILD, what is the impact of chest radiograph compared to high resolution CT thorax on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

18. In people with rheumatic disease with ILD, what is the impact of bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy) compared to no bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy) on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

19. In people with rheumatic disease with ILD, what is the impact of high resolution CT thorax compared to bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy) on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

20. In people with rheumatic disease with ILD, what is the impact of PFTs compared to 6-minute walk test distance on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

21. In people with rheumatic disease with ILD, what is the impact of PFTs and 6-minute walk test distance compared to PFTs alone on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

22. In people with rheumatic disease with ILD, what is the impact of PFTs compared to ambulatory desaturation on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

23. In people with rheumatic disease with ILD, what is the impact of PFTs and high resolution CT thorax compared to PFTs alone on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

24. In people with rheumatic disease with ILD, what is the impact of 6-minute walk test distance compared to ambulatory desaturation on responsiveness/ sensitivity to change of the test, disease-related outcomes, treatment-related serious adverse events and testing-related adverse events?

Medical Management

Rheumatic disease 1st ILD therapy

25. In people with rheumatic disease with ILD, what is the impact of mycophenolate compared to no mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

26. In people with rheumatic disease with ILD, what is the impact of cyclophosphamide compared to no cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

27. In people with rheumatic disease with ILD, what is the impact of leflunomide compared to no leflunomide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

28. In people with rheumatic disease with ILD, what is the impact of methotrexate compared to no methotrexate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

29. In people with rheumatic disease with ILD, what is the impact of azathioprine compared to no azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

30. In people with rheumatic disease with ILD, what is the impact of calcineurin inhibitors compared to no calcineurin inhibitors as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

31. In people with rheumatic disease with ILD, what is the impact of anti-TNF therapy compared to no anti-TNF therapy as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

32. In people with rheumatic disease with ILD, what is the impact of abatacept compared to no abatacept as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

33. In people with rheumatic disease with ILD, what is the impact of anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) compared to no anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

34. In people with rheumatic disease with ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to no IL-6 receptor antagonists (tocilizumab, sarilumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

35. In people with rheumatic disease with ILD, what is the impact of JAK inhibitors compared to no JAK inhibitors as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

36. In people with rheumatic disease with ILD, what is the impact of daily oral prednisone compared to no daily oral prednisone as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

37. In people with rheumatic disease with ILD, what is the impact of IV pulse glucocorticoids compared to no IV pulse glucocorticoids first line ILD treatment on disease-related outcomes and treatment-related adverse events?

38. In people with rheumatic disease with ILD, what is the impact of nintedanib compared to no nintedanib as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

39. In people with rheumatic disease with ILD, what is the impact of pirfenidone compared to no pirfenidone as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

40. In people with rheumatic disease with ILD, what is the impact of IVIG compared to no IVIG as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

41. In people with rheumatic disease with ILD, what is the impact of plasma exchange compared to no plasma exchange as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

42. In people with rheumatic disease with ILD without ILD progression, what is the impact of adding nintedanib to mycophenolate compared to not adding nintedanib to mycophenolate on disease-related outcomes and treatment-related adverse events?

43. In people with rheumatic disease with ILD without ILD progression, what is the impact of adding pirfenidone to mycophenolate compared to not adding pirfenidone to mycophenolate on disease-related outcomes and treatment-related adverse events?

44. In people with rheumatic disease with ILD, what is the impact of upfront combination of nintedanib with mycophenolate compared to mycophenolate alone as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

45. In people with rheumatic disease with ILD, what is the impact of upfront combination of pirfenidone with mycophenolate compared to mycophenolate alone as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

46. In people with rheumatic disease with ILD, what is the impact of methotrexate compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

47. In people with rheumatic disease with ILD, what is the impact of leflunomide compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

48. In people with rheumatic disease with ILD, what is the impact of azathioprine compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

49. In people with rheumatic disease with ILD, what is the impact of cyclophosphamide compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse

events?

50. In people with rheumatic disease with ILD, what is the impact of calcineurin inhibitors compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

51. In people with rheumatic disease with ILD, what is the impact of TNF inhibitors compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

52. In people with rheumatic disease with ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

53. In people with rheumatic disease with ILD, what is the impact of anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

54. In people with rheumatic disease with ILD, what is the impact of abatacept compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

55. In people with rheumatic disease with ILD, what is the impact of JAK inhibitors compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

56. In people with rheumatic disease with ILD, what is the impact of nintedinib compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

57. In people with rheumatic disease with ILD, what is the impact of pirfenidone compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

58. In people with rheumatic disease with ILD, what is the impact of IVIG compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

59. In people with rheumatic disease with ILD, what is the impact of oral prednisone compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

60. In people with rheumatic disease with ILD, what is the impact of intravenous methylprednisolone compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

61. In people with rheumatic disease with ILD, what is the impact of plasma exchange compared to mycophenolate as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

62. In people with rheumatic disease with ILD, what is the impact of methotrexate compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

63. In people with rheumatic disease with ILD, what is the impact of leflunomide compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

64. In people with rheumatic disease with ILD, what is the impact of azathioprine compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

65. In people with rheumatic disease with ILD, what is the impact of cyclophosphamide compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

66. In people with rheumatic disease with ILD, what is the impact of calcineurin inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

67. In people with rheumatic disease with ILD, what is the impact of TNF inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

68. In people with rheumatic disease with ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

69. In people with rheumatic disease with ILD, what is the impact of abatacept compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

70. In people with rheumatic disease with ILD, what is the impact of JAK inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

71. In people with rheumatic disease with ILD, what is the impact of nintedinib compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

72. In people with rheumatic disease with ILD, what is the impact of pirfenidone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

73. In people with rheumatic disease with ILD, what is the impact of IVIG compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

74. In people with rheumatic disease with ILD, what is the impact of oral prednisone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

75. In people with rheumatic disease with ILD, what is the impact of intravenous methylprednisolone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

76. In people with rheumatic disease with ILD, what is the impact of plasma exchange compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

77. In people with rheumatic disease with ILD, what is the impact of methotrexate compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

78. In people with rheumatic disease with ILD, what is the impact of leflunomide compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

79. In people with rheumatic disease with ILD, what is the impact of cyclophosphamide compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

80. In people with rheumatic disease with ILD, what is the impact of calcineurin inhibitors compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

81. In people with rheumatic disease with ILD, what is the impact of TNF inhibitors compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

82. In people with rheumatic disease with ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

83. In people with rheumatic disease with ILD, what is the impact of abatacept compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

84. In people with rheumatic disease with ILD, what is the impact of JAK inhibitors compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

85. In people with rheumatic disease with ILD, what is the impact of nintedinib compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

86. In people with rheumatic disease with ILD, what is the impact of pirfenidone compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

87. In people with rheumatic disease with ILD, what is the impact of IVIG compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

88. In people with rheumatic disease with ILD, what is the impact of oral prednisone compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

89. In people with rheumatic disease with ILD, what is the impact of intravenous methylprednisolone compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

90. In people with rheumatic disease with ILD, what is the impact of plasma exchange compared to azathioprine as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

91. In people with rheumatic disease with ILD, what is the impact of methotrexate compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

92. In people with rheumatic disease with ILD, what is the impact of leflunomide compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

93. In people with rheumatic disease with ILD, what is the impact of calcineurin inhibitors compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

94. In people with rheumatic disease with ILD, what is the impact of TNF inhibitors compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

95. In people with rheumatic disease with ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

96. In people with rheumatic disease with ILD, what is the impact of abatacept compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related

adverse events?

97. In people with rheumatic disease with ILD, what is the impact of JAK inhibitors compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

98. In people with rheumatic disease with ILD, what is the impact of nintedinib compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

99. In people with rheumatic disease with ILD, what is the impact of pirfenidone compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

100. In people with rheumatic disease with ILD, what is the impact of IVIG compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

101. In people with rheumatic disease with ILD, what is the impact of oral prednisone compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

102. In people with rheumatic disease with ILD, what is the impact of intravenous methylprednisolone compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

103. In people with rheumatic disease with ILD, what is the impact of plasma exchange compared to cyclophosphamide as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

104. In people with rheumatic disease with ILD, what is the impact of nintedanib compared to IL-6 receptor antagonists (tocilizumab, sarilumab) as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

105. In people with rheumatic disease with ILD, what is the impact of referral for stem cell transplant compared to optimal medical management as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

106. In people with rheumatic disease with ILD, what is the impact of referral for lung transplant compared to optimal medical management as first line ILD treatment on disease-related outcomes and treatment-related adverse events?

Rheumatic disease with ILD progression after any 1st ILD therapy

107. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding the combination of nintedanib and mycophenolate compared to adding mycophenolate alone on disease-related outcomes and treatment-related adverse events?

108. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding the combination of pirfenidone and mycophenolate compared to adding mycophenolate alone on disease-related outcomes and treatment-related adverse events?

109. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding methotrexate compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

110. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding leflunomide compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

111. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding azathioprine compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

112. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding cyclophosphamide compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

113. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding calcineurin inhibitors compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

114. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding TNF inhibitors compared to adding mycophenolate on disease-related outcomes and treatment-

related adverse events?

115. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding IL-6 receptor antagonists (tocilizumab, sarilumab) compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

116. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

117. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding abatacept compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

118. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding JAK inhibitors compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

119. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding nintedinib compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

120. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding pirfenidone compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

121. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding IVIG compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

122. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding oral prednisone compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

123. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding intravenous methylprednisolone compared to adding mycophenolate on disease-related

outcomes and treatment-related adverse events?

124. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding plasma exchange compared to adding mycophenolate on disease-related outcomes and treatment-related adverse events?

125. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding methotrexate compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

126. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding leflunomide compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

127. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding azathioprine compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

128. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding cyclophosphamide compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

129. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding calcineurin inhibitors compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

130. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding TNF inhibitors compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

131. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding IL-6 receptor antagonists (tocilizumab, sarilumab) compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

132. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding abatacept compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab,

ofatumumab) on disease-related outcomes and treatment-related adverse events?

133. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding JAK inhibitors compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

134. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding nintedinib compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

135. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding pirfenidone compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

136. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding IVIG compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

137. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding oral prednisone compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

138. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding intravenous methylprednisolone compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

139. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding plasma exchange compared to adding anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) on disease-related outcomes and treatment-related adverse events?

140. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding methotrexate compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

141. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding leflunomide compared to adding azathioprine on disease-related outcomes and treatment-

related adverse events?

142. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding cyclophosphamide compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

143. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding calcineurin inhibitors compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

144. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding TNF inhibitors compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

145. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding IL-6 receptor antagonists (tocilizumab, sarilumab) compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

146. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding abatacept compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

147. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding JAK inhibitors compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

148. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding nintedinib compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

149. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding pirfenidone compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

150. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding IVIG compared to adding azathioprine on disease-related outcomes and treatment-related

adverse events?

151. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding oral prednisone compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

152. In people with rheumatic disease ILD progression after 1st ILD therapy, what is the impact of adding intravenous methylprednisolone compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

153. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding plasma exchange compared to adding azathioprine on disease-related outcomes and treatment-related adverse events?

154. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding methotrexate compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

155. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding leflunomide compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

156. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding calcineurin inhibitors compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

157. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding TNF inhibitors compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

158. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding IL-6 receptor antagonists (tocilizumab, sarilumab) compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

159. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding abatacept compared to adding cyclophosphamide on disease-related outcomes and treatment-

related adverse events?

160. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding JAK inhibitors compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

161. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding nintedinib compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

162. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding pirfenidone compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

163. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding IVIG compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

164. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding oral prednisone compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

165. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding intravenous methylprednisolone compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

166. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of adding plasma exchange compared to adding cyclophosphamide on disease-related outcomes and treatment-related adverse events?

167. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of referral for stem cell transplant compared to optimal medical management on disease-related outcomes and treatment-related adverse events?

168. In people with rheumatic disease with ILD progression after 1st ILD therapy, what is the impact of referral for lung transplant compared to optimal medical management on disease-related outcomes and treatment-related adverse events?

Rheumatic disease with rapidly progressive ILD

169. In people with rheumatic disease with rapidly progressive ILD, what is the impact of daily oral prednisone compared to no daily oral prednisone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

170. In people with rheumatic disease with rapidly progressive ILD, what is the impact of pulse intravenous glucocorticoids compared to no pulse intravenous glucocorticoids as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

171. In people with rheumatic disease with rapidly progressive ILD, what is the impact of nintedanib compared to no nintedanib as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

172. In people with rheumatic disease with rapidly progressive ILD, what is the impact of pirfenidone compared to no pirfenidone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

173. In people with rheumatic disease with rapidly progressive ILD, what is the impact of adding nintedanib to mycophenolate compared to not adding nintedanib to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

174. In people with rheumatic disease with rapidly progressive ILD, what is the impact of adding pirfenidone to mycophenolate compared to not adding pirfenidone to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

175. In people with rheumatic disease with rapidly progressive ILD, what is the impact of upfront combination of nintedanib with mycophenolate compared to mycophenolate alone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

176. In people with rheumatic disease with rapidly progressive ILD, what is the impact of upfront combination of pirfenidone with mycophenolate compared to mycophenolate alone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

177. In people with rheumatic disease with rapidly progressive ILD, what is the impact of methotrexate compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes

and treatment-related adverse events?

178. In people with rheumatic disease with rapidly progressive ILD, what is the impact of leflunomide compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

179. In people with rheumatic disease with rapidly progressive ILD, what is the impact of azathioprine compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

180. In people with rheumatic disease with rapidly progressive ILD, what is the impact of cyclophosphamide compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

181. In people with rheumatic disease with rapidly progressive ILD, what is the impact of calcineurin inhibitors compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

182. In people with rheumatic disease with rapidly progressive ILD, what is the impact of TNF inhibitors compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

183. In people with rheumatic disease with rapidly progressive ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

184. In people with rheumatic disease with rapidly progressive ILD, what is the impact of anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

185. In people with rheumatic disease with rapidly progressive ILD, what is the impact of abatacept compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

186. In people with rheumatic disease with rapidly progressive ILD, what is the impact of JAK inhibitors compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes

and treatment-related adverse events?

187. In people with rheumatic disease with rapidly progressive ILD, what is the impact of nintedinib compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

188. In people with rheumatic disease with rapidly progressive ILD, what is the impact of pirfenidone compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

189. In people with rheumatic disease with rapidly progressive ILD, what is the impact of IVIG compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

190. In people with rheumatic disease with rapidly progressive ILD, what is the impact of oral prednisone compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

191. In people with rheumatic disease with rapidly progressive ILD, what is the impact of intravenous methylprednisolone compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

192. In people with rheumatic disease with rapidly progressive ILD, what is the impact of plasma exchange compared to mycophenolate as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

193. In people with rheumatic disease with rapidly progressive ILD, what is the impact of methotrexate compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

194. In people with rheumatic disease with rapidly progressive ILD, what is the impact of leflunomide compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

195. In people with rheumatic disease with rapidly progressive ILD, what is the impact of azathioprine compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line

rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

196. In people with rheumatic disease with rapidly progressive ILD, what is the impact of cyclophosphamide compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

197. In people with rheumatic disease with rapidly progressive ILD, what is the impact of calcineurin inhibitors compared to anti-CD20 (rituximab, ocrelizumab, obinutuzumab, ofatumumab) antibody as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

198. In people with rheumatic disease with rapidly progressive ILD, what is the impact of TNF inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

199. In people with rheumatic disease with rapidly progressive ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

200. In people with rheumatic disease with rapidly progressive ILD, what is the impact of abatacept compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

201. In people with rheumatic disease with rapidly progressive ILD, what is the impact of JAK inhibitors compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

202. In people with rheumatic disease with rapidly progressive ILD, what is the impact of nintedinib compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

203. In people with rheumatic disease with rapidly progressive ILD, what is the impact of pirfenidone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

204. In people with rheumatic disease with rapidly progressive ILD, what is the impact of IVIG compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

205. In people with rheumatic disease with rapidly progressive ILD, what is the impact of oral prednisone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

206. In people with rheumatic disease with rapidly progressive ILD, what is the impact of intravenous methylprednisolone compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

207. In people with rheumatic disease with rapidly progressive ILD, what is the impact of plasma exchange compared to anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab) as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

208. In people with rheumatic disease with rapidly progressive ILD, what is the impact of methotrexate compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

209. In people with rheumatic disease with rapidly progressive ILD, what is the impact of leflunomide compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

210. In people with rheumatic disease with rapidly progressive ILD, what is the impact of cyclophosphamide compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

211. In people with rheumatic disease with rapidly progressive ILD, what is the impact of calcineurin inhibitors compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

212. In people with rheumatic disease with rapidly progressive ILD, what is the impact of TNF inhibitors compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

213. In people with rheumatic disease with rapidly progressive ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

214. In people with rheumatic disease with rapidly progressive ILD, what is the impact of abatacept compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

215. In people with rheumatic disease with rapidly progressive ILD, what is the impact of JAK inhibitors compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

216. In people with rheumatic disease with rapidly progressive ILD, what is the impact of nintedinib compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

217. In people with rheumatic disease with rapidly progressive ILD, what is the impact of pirfenidone compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

218. In people with rheumatic disease with rapidly progressive ILD, what is the impact of IVIG compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

219. In people with rheumatic disease with rapidly progressive ILD, what is the impact of oral prednisone compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

220. In people with rheumatic disease with rapidly progressive ILD, what is the impact of intravenous methylprednisolone compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

221. In people with rheumatic disease with rapidly progressive ILD, what is the impact of plasma exchange compared to azathioprine as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

222. In people with rheumatic disease with rapidly progressive ILD, what is the impact of methotrexate compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

223. In people with rheumatic disease with rapidly progressive ILD, what is the impact of leflunomide compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

224. In people with rheumatic disease with rapidly progressive ILD, what is the impact of calcineurin inhibitors compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

225. In people with rheumatic disease with rapidly progressive ILD, what is the impact of TNF inhibitors compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

226. In people with rheumatic disease with rapidly progressive ILD, what is the impact of IL-6 receptor antagonists (tocilizumab, sarilumab) compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

227. In people with rheumatic disease with rapidly progressive ILD, what is the impact of abatacept compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

228. In people with rheumatic disease with rapidly progressive ILD, what is the impact of JAK inhibitors compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

229. In people with rheumatic disease with rapidly progressive ILD, what is the impact of nintedinib compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

230. In people with rheumatic disease with rapidly progressive ILD, what is the impact of pirfenidone compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

231. In people with rheumatic disease with rapidly progressive ILD, what is the impact of IVIG compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

232. In people with rheumatic disease with rapidly progressive ILD, what is the impact of oral prednisone compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

233. In people with rheumatic disease with rapidly progressive ILD, what is the impact of intravenous methylprednisolone compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

234. In people with rheumatic disease with rapidly progressive ILD, what is the impact of plasma exchange compared to cyclophosphamide as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

235. In people with rheumatic disease with rapidly progressive ILD, what is the impact of dual combination therapy* compared to monotherapy† as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

236. In people with rheumatic disease with rapidly progressive ILD, what is the impact of triple combination therapy‡ compared to monotherapy† as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

237. In people with rheumatic disease with rapidly progressive ILD, what is the impact of triple combination therapy‡ compared to dual combination therapy* as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

238. In people with rheumatic disease with rapidly progressive ILD, what is the impact of using IVIG and/or plasma exchange in addition to monotherapy†, dual combination therapy*, or triple combination therapy‡ compared to using monotherapy†, dual combination therapy*, or triple combination therapy‡ alone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

239. In people with rheumatic disease with rapidly progressive ILD, what is the impact of using an antifibrotic (e.g., nintedanib or pirfenidone) in addition to monotherapy†, dual combination therapy*, or triple combination therapy‡ compared to using monotherapy†, dual combination therapy*, or triple

combination therapy‡ alone as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

240. In people with rheumatic disease with rapidly progressive ILD, what is the impact of referral for stem cell transplant compared to optimal medical management as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

241. In people with rheumatic disease with rapidly progressive ILD, what is the impact of referral for lung transplant compared to optimal medical management as first line rapidly progressive ILD treatment on disease-related outcomes and treatment-related adverse events?

† Monotherapy examples: oral prednisone/intravenous methylprednisolone, or mycophenolate, or azathioprine, or a calcineurin inhibitor, or rituximab, or cyclophosphamide

* Dual combination therapy examples: oral prednisone/intravenous methylprednisolone and mycophenolate, or oral prednisone/intravenous methylprednisolone and azathioprine, or oral prednisone/intravenous methylprednisolone and a calcineurin inhibitor, or oral prednisone/intravenous methylprednisolone and rituximab, or oral prednisone/intravenous methylprednisolone and cyclophosphamide, or oral prednisone/intravenous methylprednisolone and a JAK inhibitor

‡ Triple combination therapy examples: oral prednisone/intravenous methylprednisolone and rituximab and cyclophosphamide, or oral prednisone/intravenous methylprednisolone and cyclophosphamide and a calcineurin inhibitor, or oral prednisone/intravenous methylprednisolone and mycophenolate and a calcineurin inhibitor, or oral prednisone/intravenous methylprednisolone and mycophenolate and abatacept, or oral prednisone/intravenous methylprednisolone and rituximab and mycophenolate

APPENDIX B – INCLUSION/EXCLUSION CRITERIA

POPULATIONS

Include

- Adults
- Rheumatoid arthritis, Systemic sclerosis (Scleroderma), Mixed Connective Tissue Disease (MCTD), Polymyositis, Dermatomyositis, MDA5 Dermatomyositis, Immune Mediated Necrotizing Myositis, Antisynthetase syndrome, Sjogren's syndrome
- Progressive Fibrosing ILD

Exclude

- Pediatrics (age 16 or younger)
- Juvenile scleroderma, juvenile systemic sclerosis, juvenile dermatomyositis, juvenile idiopathic arthritis
- Sarcoidosis, Interstitial Pneumonia with Autoimmune Features (IPAF), ankylosing spondylitis, ANCA-associated vasculitis, Systemic lupus erythematosus, Undifferentiated connective tissue disease
- Idiopathic Pulmonary Fibrosis
- Idiopathic interstitial pneumonias
- Unclassifiable ILD
- Overlap syndromes (e.g., SSc+myositis, RA+SSc, et)

INTERVENTIONS

Include

- Pulmonary Function Tests (PFTs)
- History/physical alone (e.g., shortness of breath (dyspnea), functional class and physician examination: crackles on auscultation)
- High resolution CT Thorax
- 6-minute walk test distance
- Ambulatory desaturation
- Chest radiograph (chest x-ray)
- Bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy)
- Surgical lung biopsy
- csDMARDs: methotrexate, leflunomide, azathioprine, cyclophosphamide, mycophenolate, calcineurin inhibitors (tacrolimus, cyclosporine)
- bDMARDs: TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), IL-6 receptor antagonists (tocilizumab, sarilumab), anti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab), abatacept

- tsDMARDs: JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
- Others: Oral prednisone, intravenous methylprednisolone, intravenous immunoglobulin (IVIG), plasma exchange (plasmapheresis)
- Antifibrotics: Pirfenidone, Nintedanib
- Stem cell transplant (autologous, mesenchymal stem cells, hematopoietic, myeloablative, non-myeloablative)
- Lung Transplant

Exclude

- Vaccines: influenza, COVID-19, MMR, pneumococcus vaccine (refer to 2022 ACR vaccine guideline, presently in journal review; summary is online)
- Education (self-management of oxygen, ILD disease) *(will mention in Introduction or Discussion section)*
- Physiotherapy (chest physiotherapy, airway clearance, incentive spirometry), Exercise (aerobic, resistance training, yoga, tai chi), Pulmonary Rehabilitation (cardio-pulmonary rehabilitation, resistance training, in a center versus home)
- Oxygen (oxygen desaturation at rest, oxygen desaturation <88% with exercise)
- Palliative care (cough, pain, air hunger, end stage, end of life planning, when to initiate, what to initiate)
- Smoking cessation
- Fundoplication
- GI medications: proton pump inhibitors, H2 blockers, promotility agents
- Ibritumomab (is anti-CD20, but it is radioimmunotherapy)
- Basiliximab

COMPARATORS

Include

- No test
- History/physical alone (e.g., shortness of breath (dyspnea), functional class and physician examination: crackles on auscultation)
- High resolution CT Thorax
- Bronchoscopy (may include broncho-alveolar lavage, transbronchial biopsy, cryobiopsy)
- 6-minute walk test distance
- Ambulatory desaturation
- PFTs
- Placebo, no treatment
- Mycophenolate
- antiAnti-CD20 antibody (rituximab, ocrelizumab, obinutuzumab, ofatumumab)
- Azathioprine
- Cyclophosphamide

- Stem cell transplant (autologous, mesenchymal stem cells, hematopoietic, myeloablative, non-myeloablative)
- Lung transplant

OUTCOMES *(see Appendix C)*

STUDY DESIGN (includes only studies published in English language)

For all PICO questions, we will include randomized or non-randomized controlled trials (this includes case-control studies). To capture adverse events, we will also consider open-label extension studies of RCTs or other longitudinal observational studies that focus on safety and tolerability. For PICO questions that focus on assessing the accuracy of screening tools, we will also include studies without an independent control group, specifically cohort and cross-sectional studies. We will also include existing systematic reviews and guidelines from other societies **only** to confirm that we have included all relevant reference.

Include

- RCTs, including:
  - Open-label extensions of RCTs with placebo involved
- Non-randomized controlled studies, including
  - Case-control studies
- Cohort studies
- Cross-sectional studies
- Longitudinal studies (focusing on safety and tolerability)
- Systematic reviews and Guidelines from other societies

[NOTE: If there has been a recently done, well-done systematic review on the exact PICO that ACR is asking, then that systematic review could be considered for use in the guideline; primary study data would still need to be pulled in the ACR's database, though.]

Exclude

- Abstracts
- Case reports
- Narrative reviews
- Prevalence studies
- Economic studies, e.g., cost-effectiveness studies
- Drug adherence studies
- Studies of risk factors
- Foreign language studies
- Studies with irrelevant population, interventions, or outcomes
- Animal studies

APPENDIX C: OUTCOMES

Screening

Critical outcomes:

- Diagnostic accuracy
- Disease-related outcomes[1]
- Diagnostic testing-related adverse events

Monitoring

Critical outcomes:

- Responsiveness/sensitivity to change of the test
- Disease-related outcomes[1]
- Treatment-related serious adverse events
- Testing-related adverse events

Medical management

- Disease-related outcomes[1]
- Treatment-related adverse events

[1]**Critical outcomes:** mortality, disability, health related quality of life, adverse events (serious adverse events, toxicity leading to discontinuation). **Surrogate outcomes:** disease activity/disease progression defined by forced vital capacity (FVC), diffusion capacity for carbon monoxide (DLCO), CT thorax: extent of disease, disease progression.

APPENDIX D: DISCLOSURES

Participant Disclosures - American College of Rheumatology (ACR) Guideline for the Screening, Monitoring, and Treatment of Interstitial Lung Disease in Patients with Systemic Autoimmune Rheumatic Disease

In order for the College to most effectively further its mission and to otherwise maintain its excellent reputation in the medical community and with the public, it is important that confidence in the College's integrity be maintained. The cornerstone of the ACR's Disclosure Policy is disclosure of actual and potential conflicts so that they can be evaluated by the College in order to avoid undue influence of potential conflicts. The purpose of the ACR's Disclosure Policy is identification of relationships which may pose actual or potential conflicts. These actual or potential conflicts can then be evaluated by the College so that adjustments can be made that will avoid any undue influence. This policy is based on the principle that, in many cases, full disclosure of the actual or potentially conflicting relationship will of itself suffice to protect the integrity of the College and its interests.

Participants	Role	Primary Employer	Interest Held By	Interest Type	Entity/Licensee	Additional Information	Value
Sindhu R. Johnson	Core Team – PI	Toronto Western Hospital	Self	Independent Contractor - Editorial Board	Best Practice and Clinical Rheumatology		
			Self	Independent Contractor - Associate Editor	Journal of Rheumatology		
			Spouse/Partner	Independent Contractor - Editorial Board Member	Anesthesiology		
			Spouse/Partner	Independent Contractor - Editorial Board Member	Canadian Journal of Anesthesia		
			Spouse/Partner	Independent Contractor - Consultant	Edwards Lifesciences		
			Spouse/Partner	Independent Contractor - Consultant	Surgical Safety Technologies		
			Spouse/Partner	Independent Contractor - Editorial Board Member	Circulation Journal		
Elana Bernstein	Core Team - Co-first author	Columbia University/New York-Presbyterian Hospital	Self	Grant / Contract	U.S. Department of Defense		$750,000.00
			Self	Employment	James J. Peters VA Medical Center		
			Self	Employment	Columbia University		
			Self	Grant / Contract	Scleroderma Research Foundation	Columbia receives fees from the Scleroderma Research Foundation based on the number of new patient study visits and follow-up patient	$52,000.00

						study visits conducted.	
			Self	Grant / Contract	National Institutes of Health		$801,500.00
			Self	Independent Contractor - IC Iloprost for SSc-associated Raynaud's	Eicos	Total direct costs: $16,358.19 per patient	
			Self	Independent Contractor - Data And Safety Monitoring	UCLA Health System		$20,000.00
			Self	Independent Contractor - A Phase 2, Open-label, Multicenter Study to Evaluate the Efficacy and Safety of Belumosudil in dcSSc	Kadmon Pharmaceuticals LLC	Total direct costs: $40,697 per patient	
			Self	Grant / Contract	Boehringer Ingelheim		$500,000.00
			Self	Independent Contractor - Consultant	Boehringer Ingelheim		$6,526.25
			Self	Grant / Contract	Pfizer		$150,000.00
			Self	Independent Contractor - Scientific Advisory Board	Boehringer Ingelheim	I did not accept any compensation for participating in this Scientific Advisory Board.	

Marcy B. Bolster	Core Team - Content expert	Massachusetts General Hospital	Self	Grant / Contract	Genentech	Clinical trial I helped with data collection but did not receive salary support from this trial. I am not privy to the contracted amount. I thought I should disclose my relationship since my name is listed as a co-investigator and co-author on the publication. Please let me know if additional information is needed.	$1.00
			Self	Grant / Contract	Cumberland Pharmaceuticals	I am a co-investigator for this clinical trial	$31,699.00
			Self	Independent Contractor - Consultant	Merck Sharp & Dohme Corporation		
			Self	Independent Contractor - Associate Editor	PracticeUpdate		$10,000.00
			Self	Independent Contractor - Member, ABIM Rheumatology Longitudinal Assessment Program (LAP)Approval Committee	American Board of Internal Medicine		
			Self	Independent Contractor - Co-investigator	Corbus		
			custodial account with child who is no longer a dependent	Stock	Johnson and Johnson		$5,000.00
			Self	Independent Contractor - Principal Investigatory	Rheumatology Research Foundation	Grant recipient for salary support	
			Self	Independent Contractor - Principal Investigatory	Rheumatology Research Foundation	Grant recipient for salary support	

Jonathan H. Chung	Core Team - Content expert	University of Chicago				Nothing to disclose	
Sonye Danoff	Core Team - Content expert	Johns Hopkins University School of Medicine	Self	Grant / Contract	Boehringer Ingelheim	Open label extension of INBUILD clinical trial	$15,000.00
			Self	Grant / Contract	Boehringer Ingelheim		$500,000.00
			Self	Independent Contractor - Consultant	CSL Behring	This is a 4- hour virtual multi-disciplinary advisory board on autoimmune myositis	$3,000.00
			Self	Grant / Contract	Bristol Myers Squibb Company	This is a clinical trial of an LPA inhibitor in Progressive-fibrosing ILD	$125,000.00
			Self	Independent Contractor - Consultant	Boehringer Ingelheim		$2,600.00
			Self	Independent Contractor - Data And Safety Monitoring	Galapagos		$1,000.00
			Self	Employment	Pulmonary Fibrosis Foundation		
			Self	Fiduciary Officer	American Thoracic Society		
Michael George	Core Team - Content expert	Penn Medicine	Self	Independent Contractor - Consultant	AbbVie		$4,085.00
			Self	Employment	Perelman School of Medicine, University of Pennsylvania		
			Self	Independent Contractor - Consultant	Global Healthy Living Foundation		
			Self	Grant / Contract	GlaxoSmithKline		$61,000.00
			Self	Independent Contractor - Consultant	Dysimmune Diseases Foundation		$2,600.00
			Self	Independent Contractor - Consultant	Global Healthy Living Foundation		$3,000.00
Dinesh Khanna	Core Team - Content expert	University of Michigan	Self	Independent Contractor - Consultant	Genentech Foundation		$4,000.00
			Self	Independent Contractor - Consultant	CSL Behring		$1,000.00
			Self	Independent Contractor - Consultant	AbbVie		$4,000.00
			Self	Independent Contractor - Consultant	Actelion Pharmaceuticals		$6,000.00
			Self	Independent Contractor - Consultant	Prometheus		$5,000.00

			Self	Independent Contractor - Consultant	Horizon Pharma plc		$20,000.00
			Self	Stock Option	Eicos Sciences	Chief Medical Officer	
			Self	Independent Contractor - Consultant	Boehringer Ingelheim		$80,000.00
Ilya Ivlev	Core Team - Literature Review Co-Leader	ECRI Institute	Self	Grant / Contract	U.S. Department of Defense	Role-co-lead	$0.00
			Self	Grant / Contract	Agency for Healthcare Research and Quality	Goal 1: The purpose of this Task Order is to conduct systematic evidence reviews that the Task Force will use to make new or update existing recommendations Goal 2: To synthesize available evidence to support primary care guidelines development.	$0.00
			Self	Independent Contractor - Affiliate Investigator	Kaiser Permanente		
			Self	Grant / Contract	National Institute on Aging		$60,000.00
			Self	Employment	ECRI		
			Self	Grant / Contract	National Cancer Institute	To synthesize available evidence to support primary care guidelines development. Role: Research Curator, evidence synthesis for actionability	$0.00
			Self	Employment	Kaiser Permanente		
			Self	Grant / Contract	Agency for Healthcare Research and Quality		$300,000.00

Stacey Uhl	Core Team - Literature Review Co-Leader	ECRI Institute				Nothing to disclose	
Gordon Guyatt	Core Team - GRADE Expert	McMaster University				Nothing to disclose	
Reza Mirza	Core Team - GRADE/Methodological Contributor	McMaster University				Nothing to disclose	
Sandeep Agarwal	Lit Review Team	Baylor College of Medicine				Nothing to disclose	
Danielle Antin-Ozerkis	Lit Review Team	Yale School of Medicine	Self	Grant / Contract	Pliant Therapeutics	Grant paid to institution for work completed, patients enrolled	$130,999.00
			Self	Grant / Contract	Galacto Biotech AB	Grant paid to institution for work completed, patients enrolled	$116,975.00
			Self	Grant / Contract	Galapagos	Grant paid to institution for work completed, patients enrolled	$181,000.00
			Self	Grant / Contract	FibroGen	Grant paid to institution for work completed, patients enrolled	$133,000.00
			Self	Stock	Amgen		$100,000.00
			Self	Grant / Contract	Boehringer Ingelheim	Grant paid to institution for work completed, patients enrolled	$126,683.00
			Self	Grant / Contract	Boehringer Ingelheim	Grant paid to institution for work completed, patients enrolled	$120,811.00
			Self	Stock	Pfizer		$15,000.00
			Self	Stock	AbbVie		$100,000.00

			Self	Grant / Contract	Genentech	Grant paid to institution for work completed, patients enrolled	$211,000.00
Bradford Bemiss	Lit Review Team	Loyola University Medical Center	Self	Independent Contractor - Speakers bureau	Boehringer Ingelheim		
Vaidehi Chowdhary	Lit Review Team	Yale School of Medicine	Self	Independent Contractor - International Editor	International Journal of Rheumatic Diseases		
			Self	Grant / Contract	MCIC vermont	Title: Communication and Management of Test Results in Patients Initiating Biologic Agents PI on the Grant awarded to the section. No compensation for salary, or consultation. No effort paid for self.	$75,000.00
			Self	Independent Contractor - International editorial board member	Indian Journal of Rheumatology		
Jane E. Dematte D'Amico	Lit Review Team	Northwestern Medicine	Self	Independent Contractor - Site Principal Investigator	United Therapeutics Corporation		
			Self	Independent Contractor - Site Principle Investigator	FibroGen		
			Self	Independent Contractor - Site Prinicipal Investigator	Genentech		
			Self	Independent Contractor - Site Principal Investigator	Boehringer Ingelheim		
Robert Hallowell	Lit Review Team	Massachusetts General Hospital	Self	Independent Contractor - Consultant	Genentech		$4,000.00
			Self	Independent Contractor - Consultant	Boehringer Ingelheim		$2,500.00
			Self	Independent Contractor - Consultant	Boehringer Ingelheim		$5,000.00
			Self	Medical Advisory board for the Myositis Association.			

Alicia M. Hinze	Lit Review Team	Mayo Clinic	Contract with my Employer Mayo Clinic	Grant / Contract	Rheumatology Research Foundation	Career development award which supports engagement in research and career development activities to evaluate radiomic biomarkers for ILD progression in systemic sclerosis.	$375,000.00
			Self	Grant / Contract	Mayo Clinic	Career Development Award supporting 0.1FTE and some research expenses	$150,000.00
			Self	Employment	Mayo Clinic	Division of Rheumatology, full time, hybrid research and clinical position	
Patil A. Injean	Lit Review Team	Cedars-Sinai				Nothing to disclose	
Nikhil Jiwrajka	Lit Review Team	Penn Medicine	Self	Grant / Contract	Perelman School of Medicine, University of Pennsylvania		$15,000.00
			Self	Employment	Perelman School of Medicine, University of Pennsylvania		
			Self	Grant / Contract	Perelman School of Medicine, University of Pennsylvania		$40,000.00
Elena Joerns	Lit Review Team	UT Southwestern Medical Center	Self	Employment	University of Texas Southwestern Medical Center		
			Self	Grant / Contract	Pfizer Inc.	22.7% effort	$50,000.00

			T32 training grant supporting Elena Joerns' salary	Grant / Contract	National Institute of Health	The major goals of this project are to perform a detailed phenotypic analysis of immunosuppressed patients with interstitial pneumonia with autoimmune features in the UTSW cohort and assess predictors of response to immunosuppression.	$259,496.00
Joyce Lee	Lit Review Team	University of Colorado	Self	Independent Contractor - Consultant	Boehringer Ingelheim		$1,200.00
			Self	Grant / Contract	Boehringer Ingelheim	Only start up costs have been received, the milestone based payment of the remainder of the grant has been delayed due to the pandemic.	$500,000.00
			Self	Grant / Contract	Boehringer Ingelheim	Aryeh Fischer was site PI originally, transferred to me beginning August 2019 after his departure	$128,954.00
			Self	Grant / Contract	Bristol-Myers Squibb		$18,320.00
			Self	Grant / Contract	Boehringer Ingelheim	my role is co-investigator	$491,453.00
			Self	Grant / Contract	Novartis		$71,253.00
			Self	Independent Contractor - Consultant	Pulmonary Fibrosis Foundation	They support 25% of my time	

			Self	Grant / Contract	FibroGen		$30,455.00
			Self	Grant / Contract	U.S. Department of Defense	my role is co-investigator	$9,969,396.00
			Self	Employment	Pulmonary Fibrosis Foundation	They support 25% of my time	
			Self	Grant / Contract	National Heart, Lung, and Blood Institute		$576,298.00
			Self	Independent Contractor - Consultant	ElevenP15		$6,000.00
			Self	Independent Contractor - Data And Safety Monitoring	United Therapeutics Corporation		$1,000.00
			Self	Independent Contractor - Data And Safety Monitoring	SyneosHealth		$2,000.00
			Self	Independent Contractor - Member of the ILD editorial board	Chest Journal		
			Self	Employment	university of Colorado school of medicine		
			Self	Grant / Contract	UCLA Health System	Aryeh Fischer was site PI originally, transferred to me beginning August 2019 after his departure	$93,553.00
			Self	Grant / Contract	National Heart, Lung, and Blood Institute	My role is co-investigator	$6,195,411.00
			Self	Independent Contractor - Co-chair of program committee	American Thoracic Society		
			Self	Grant / Contract	Galapagos	close out ongoing	$33,291.00
			Self	Independent Contractor - Consultant	United Therapeutics Corporation		$800.00

Ashima Makol	Lit Review Team	Mayo Clinic	Self	Independent Contractor - Co-investigator for clinical trial sub study	Boehringer Ingelheim	No compensation. Nailfold capillaroscopy substudy complete more than 2 years ago. SENSCIS-ON participants are seen periodically for physical exams.	
			Self	Employment	Mayo Clinic		
			Self	Independent Contractor - Site PI for the KD025-209 study	Kadmon Corporation LLC	No personal compensation. Costs are study execution costs on site. Trial recently closed to recruitment by Sanofi. No further recruitment activity at our site.	$22,630.00
			Self	Independent Contractor - Medical content contributor	Figure1		$1,300.00
			Self	Independent Contractor - HZN-825 in Patients With Diffuse Cutaneous Systemic Sclerosis	Horizon Therapeutics plc	Phase Study is not active yet but plan to activate april/may 2022 at our site.	
Gregory McDermott	Lit Review Team	Massachusetts General Hospital	Self	Employment	Partners Healthcare		
			Self	Employment	Brigham and Women's Hospital	Clinical Fellow	
Jake G Natalini	Lit Review Team	NYU Langone Health				Nothing to disclose	
Justin Oldham	Lit Review Team	University of California, Davis	Self	Independent Contractor - Consultant	Boehringer Ingelheim		$20,000.00
			Self	Independent Contractor - Consultant	United Therapeutics Corporation		$3,000.00
			Self	Independent Contractor - Consultant	F. Hoffmann-La Roche		$5,800.00
			Self	Independent Contractor - Consultant	Lupin Pharmaceuticals, Inc		$5,000.00
Didem Saygin	Lit Review Team	University of Chicago				Nothing to disclose	

Kimberly Showalter Lakin	Lit Review Team	Hospital for Special Surgery, Weill Cornell Medicine				Nothing to disclose	
Namrata Singh	Lit Review Team	University of Washington	Self	Grant / Contract	American Heart Association		$200,000.00
			Self	Grant / Contract	Rheumatology Research Foundation		$375,000.00
Joshua J. Solomon	Lit Review Team	National Jewish Health	Self	Independent Contractor - Investigator Initiated Grant Funding	Boehringer Ingelheim	30,000 total grant funding for 2022	$30,000.00
			Self	Independent Contractor - CTD ILD education	Boehringer Ingelheim		$6,000.00
			Self	Independent Contractor - PI TRAIL1 Trial	Genentech		$14,000.00
			Self	Grant / Contract	PFIZER CANADA INC		$82,904.00
Jeffrey Sparks	Lit Review Team	Brigham and Women's Hospital	Self	Independent Contractor - Consultant	Amgen		
			Self	Independent Contractor - Consultant	Bristol-Myers Squibb		
			Self	Independent Contractor - Consultant	AbbVie		
Marat Turgunbaev	Lit Review Team	American College of Rheumatology				Nothing to disclose	
Samera Vaseer	Lit Review Team	University of Oklahoma				Nothing to disclose	
Rohit Aggarwal	Voting Panel	University of Pittsburgh Medical Center	Self	Independent Contractor - Consultant	Scipher		
			Self	Intellectual Property - Other Intellectual Property		Under University of Pittsburgh	
			Self	Independent Contractor - Consultant	Kezar		
			Self	Independent Contractor - Consultant	Alexion Pharmaceuticals, Inc.		
			Self	Independent Contractor - Consultant	E.R. Squibb & Sons, L.L.C.		
			Self	Grant / Contract	E.R. Squibb & Sons, L.L.C.		$148,531.84
			Self	Independent Contractor - Consultant	Galapagos		
			Self	Independent Contractor - Consultant	Mallinckrodt LLC		
			Self	Independent Contractor - Consultant	argenx		
			Self	Independent Contractor - Consultant	EMD Serono		
			Self	Independent Contractor - Consultant	corbus		
			Self	Independent Contractor - Consultant	kyverna		
			Self	Independent Contractor - Consultant	Horizon Therapeutics plc		

			Self	Independent Contractor - Consultant	Merck		
			Self	Grant / Contract	Mallinckrodt Hospital Products Inc.		
			Self	Grant / Contract	Q32		$10,000.00
			Self	Independent Contractor - Consultant	AstraZeneca Pharmaceuticals LP		
			Self	Independent Contractor - Consultant	Roivant		
			Self	Grant / Contract	Mallinckrodt LLC		$75,000.00
			Self	Grant / Contract	EMD Serono		$10,000.00
			Self	Independent Contractor - Consultant	Q32		
			Self	Independent Contractor - Consultant	Janssen Global Services, LLC		
			Self	Independent Contractor - Consultant	CSL Behring		
			Self	Independent Contractor - Consultant	Janssen Biotech, Inc.		
			Self	Independent Contractor - Consultant	AbbVie Inc.		
			Self	Independent Contractor - Consultant	Teva Pharmaceutical Industries		
			Self	Independent Contractor - Consultant	Boehringer Ingelheim Pharmaceuticals, Inc.		
			Self	Independent Contractor - Consultant	Octapharma USA, Inc.		
			Self	Independent Contractor - Consultant	Pfizer		
Shervin Assassi	Voting Panel	Texas Health Science Center Houston	Self	Grant / Contract	National Institute of Health		$783,582.00
			Self	Independent Contractor - Section Editor	Current Opinions in Rheumatology		
			Self	Grant / Contract	Scleroderma Research Foundation		$467,797.00
			Self	Independent Contractor - Editorial Board	Arthritis Research and Therapy		
			Self	Grant / Contract	National Institute of Health		$1,710,960.00
			Self	Independent Contractor - Speaker bureau	Integrity continuous education		$2,500.00
			Self	Employment	The University of Texas Health Science Center at Houston		
			Self	Grant / Contract	National Institute of Health		$346,497.00
			Self	Independent Contractor - Consultant	AstraZeneca		$4,296.00
			Self	Independent Contractor - Speaker	North Carolina Rheumatology Association		$4,000.00

			Self	Independent Contractor - President	scleroderma clinical trial consortium	This is a non-profit, global organization for improving quality of clinical research in systemic sclerosis.	
			Self	Independent Contractor - Consultant	Boehringer Ingelheim	I have not yet received any compensation yet but the estimated compensation for 2022 is $15,000 to $20,000.	
			Self	Grant / Contract	Boehringer Ingelheim		$127,084.00
			Self	Grant / Contract	Boehringer Ingelheim		$108,383.00
			Self	Independent Contractor - Consultant	Boehringer Ingelheim		$21,465.59
			Self	Independent Contractor - Consultant	CSL Behring		$2,115.00
			Self	Grant / Contract	Janssen Biotech, Inc.		$246,254.00
			Self	Independent Contractor - Consultant	AbbVie		$2,250.00
Lenore Buckley	Voting Panel	Yale School of Medicine				Nothing to disclose	
Paul F. Dellaripa	Voting Panel	Brigham and Women's Hospital	Self	Independent Contractor - committee member	Food and Drug Administration		
			Self	Independent Contractor - Clincal investigator	Genentech		
			Self	Independent Contractor - Clincal investigator	Bristol-Myers Squibb	no payment of money to me	
			Self	Independent Contractor - committee member	Boehringer Ingelheim		
Robyn T. Domsic	Voting Panel	University of Pittaburgh Medical Center	Self	Independent Contractor - Consultant	CSL Behring		
Tracy Doyle	Voting Panel	Brigham and Women's Hospital	Self	Grant / Contract	Genentech	Site PI for TRAIL1 clinical trial (0.12 calendar months or 1% effort). $9,750 total cost, $7,500 direct cost per year.	$9,750.00

Tracy M. Frech	Voting Panel	Vanderbilt University Medical Center				Nothing to disclose	
Monique E. Hinchcliff	Voting Panel	Yale School of Medicine	Self	Grant / Contract	Boehringer Ingelheim		$950,231.00
Cheilonda Johnson	Voting Panel	Penn Medicine				Nothing to disclose	
Jeffrey P. Kanne	Voting Panel	University of Wisconsin School of Medicine and Public Health	Self	Independent Contractor - Consultant	Calyx.ai	Independent reviewer for clinical trials - 1 hour per week	$15,000.00
			Self	Independent Contractor - Consultant	Bayer Healthcare	Intermittent clinical trial work	$5,000.00
			Self	Independent Contractor - Consultant	Elsevier		$1,000.00
			Self	Independent Contractor - Consultant	Delfi Diagnostics	$350 per hour up to 20 hours	$475.00
			Self	Independent Contractor - Consultant	Wolters Klewer Health, Inc.		$3,000.00
John S. Kim	Voting Panel	University of Virginia School of Medicine	Self	Grant / Contract	Pulmonary Fibrosis Foundation		$50,000.00
			Self	Grant / Contract	National Heart, Lung, and Blood Institute		$171,612.00
Scott Matson	Voting Panel	University of Kansas Medical Center	Self	Employment	School of Medicine, University of Kansas		
			Self	Independent Contractor - Consultant	imvaria diagnostics		
Zsuzsanna McMahan	Voting Panel	Johns Hopkins University School of Medicine	Self	Grant / Contract	Jerome L. Greene Foundation		$50,000.00
			Self	Grant / Contract	National Institute of Health		$149,703.00
			Self	Grant / Contract	Corbus Pharmaceuticals Holdings	I was a sub-PI who did skin biopsies; I did get salary support for each biopsy I perform (~1% total)	$1,200.00
			Self	Independent Contractor - ACR Representative to the Ex Officio Advisory Board	World Scleroderma Foundation		
			Self	Intellectual Property - Other Intellectual Property			

Lee Shapiro	Voting Panel	Albany Medical College				Nothing to disclose	
Christine D. Sharkey	Voting Panel	University of Wisconsin School of Medicine and Public Health				Nothing to disclose	
Ross S. Summer	Voting Panel	Thomas Jefferson University Hospital	Self	Independent Contractor - Horizon Trial IPF	Horizon Pharma plc		
John Varga	Voting Panel	University of Michigan	Self	Independent Contractor - Consultant	Emerald pharma		
			Self	Independent Contractor - Consultant	up to date		
			Self	Independent Contractor - editor	current rheumatology reports		
			Self	Independent Contractor - Consultant	Boehringer Ingelheim		$4,000.00
			Self	Independent Contractor - Consultant	Best doctors		
			Self	Independent Contractor - EIC	WILEY		$5,000.00
			Self	Independent Contractor - Consultant	Boehringer Ingelheim		
			Self	Independent Contractor - Consultant	TeneoBio Pharma		$20,000.00

American College of Rheumatology
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Arthritis & Rheumatology
Vol. 73, No. 1, January 2021, pp 12–20
DOI 10.1002/art.41562
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Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis, and Treatment of Lyme Disease

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This evidence-based clinical practice guideline for the prevention, diagnosis, and treatment of Lyme disease was developed by a multidisciplinary panel representing the Infectious Diseases Society of North American (IDSA), the American Academy of Neurology (AAN), and the American College of Rheumatology (ACR). The scope of this guideline includes prevention of Lyme disease,

This guideline was jointly developed by the Infectious Diseases Society of America, the American Academy of Neurology Institute, and the American College of Rheumatology. The article was peer reviewed by *Arthritis & Rheumatology* and simultaneously published by *Clinical Infectious Diseases*, *Neurology*, *Arthritis Care & Research*, and *Arthritis & Rheumatology*. Each editor of the 4 journals appointed 1 reviewer for peer review. The articles

and the diagnosis and treatment of Lyme disease presenting as erythema migrans, Lyme disease complicated by neurologic, cardiac, and rheumatologic manifestations, Eurasian manifestations of Lyme disease, and Lyme disease complicated by coinfection with other tick-borne pathogens. This guideline does not include comprehensive recommendations for babesiosis and tick-borne rickettsial infections, which are published in separate guidelines. The target audience for this guideline includes primary care physicians and specialists caring for this condition such as infectious diseases specialists, emergency physicians, internists, pediatricians, family physicians, neurologists, rheumatologists, cardiologists, and dermatologists in North America.

Summarized below are the 2020 recommendations for the prevention, diagnosis, and treatment of Lyme disease. The panel followed a systematic process used in the development of other Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR) clinical practice guidelines, which included a standardized methodology for rating the certainty of the evidence and strength of recommendation using the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation) (see Figure 1). A detailed description of background, methods, evidence summary and rationale that support each recommendation, and knowledge gaps can be found online in the full text (http://onlinelibrary.wiley.com/doi/10.1002/art.41562/abstract).

I. Which measures should be used to prevent tick bites and tick-borne infections?

A. Personal protective measures

Recommendation:

1. Individuals at risk of exposure should implement personal protective measures to reduce the risk of tick exposure and infection with tick-borne pathogens *(good practice statement).*

B. Repellents to prevent tick bites

Recommendation:

1. For the prevention of tick bites, we recommend N, N-Diethyl-meta-toluamide (DEET), picaridin, ethyl-3-(N-n-butyl-N- acetyl) aminopropionate (IR3535), oil of lemon eucalyptus (OLE), p-methane-3,8-diol (PMD), 2-undecanone, or permethrin *(strong recommendation, moderate-quality evidence)*.

C. Removal of attached ticks

Recommendations:

1. We recommend promptly removing attached ticks by mechanical means using a clean fine-tipped tweezer (or a comparable device) inserted between the tick body and the skin *(good practice statement)*.
2. We recommend against burning an attached tick (with a match or other heat device) or applying noxious chemicals or petroleum products to coax its detachment *(good practice statement)*.

II. Which diagnostic tests should be used following a tick bite?

A. Diagnostic tick testing

Recommendations:

1. We recommend submitting the removed tick for species identification *(good practice statement)*.

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are identical except for minor stylistic and spelling differences in keeping with each journal's style. The full guideline is available at http://onlinelibrary.wiley.com/doi/10.1002/art.41562/abstract.

Support for this guideline was provided by the Infectious Diseases Society of America, the American Academy of Neurology, and the American College of Rheumatology.

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Conflict of interest information appears at the end of the text.

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Submitted for publication August 21, 2019; accepted in revised form June 5, 2020.

[Correction added on 11 December, 2020 after first online publication: a paragraph was inserted on page 1, prior to the existing first paragraph.]

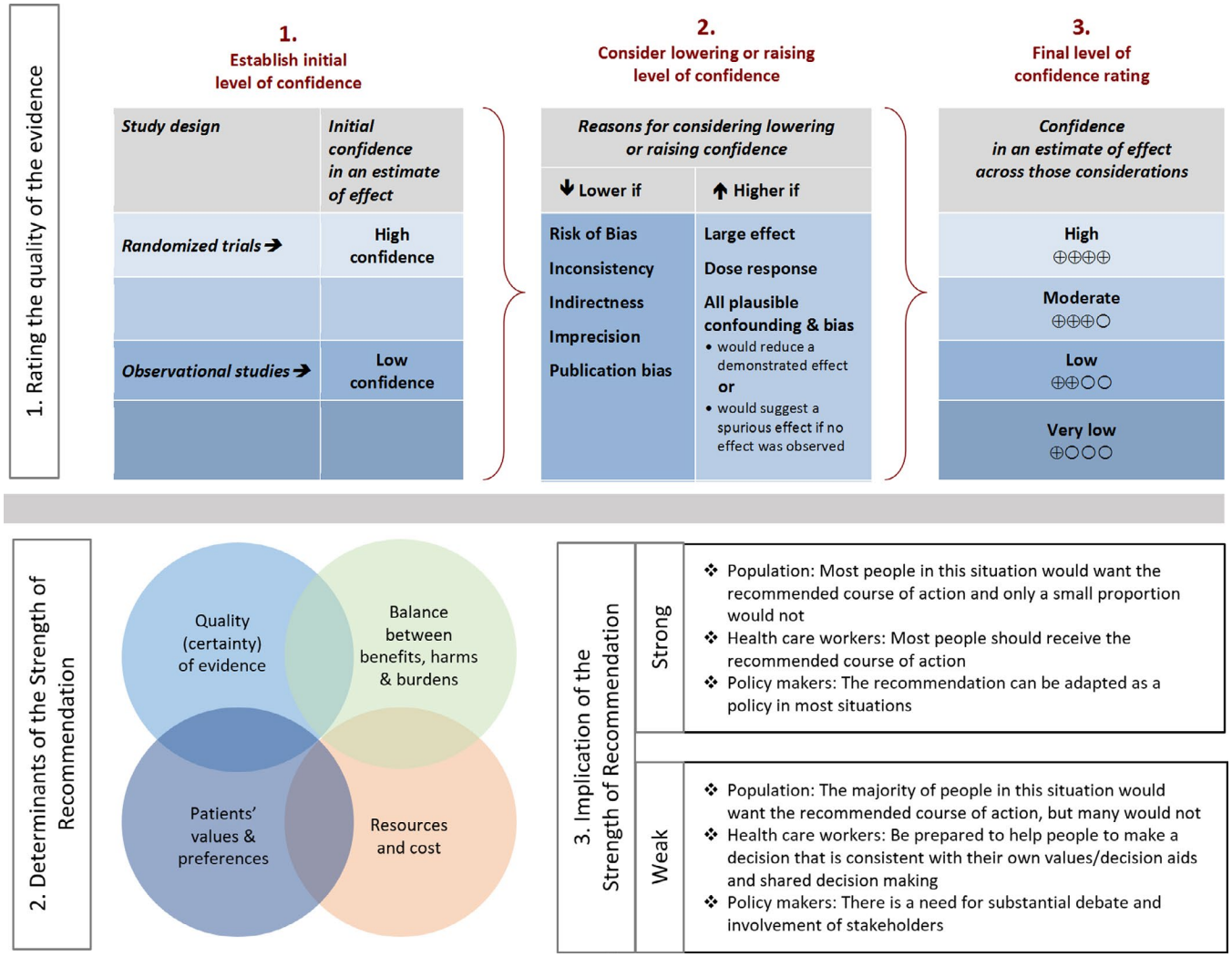
1. Rating the quality of the evidence
1.
Establish initial level of confidence
Study design
Initial confidence in an estimate of effect
Randomized trials
High confidence
Observational studies
Low confidence
2.
Consider lowering or raising level of confidence
Reasons for considering lowering or raising confidence
Lower if
Higher if
Risk of Bias
Inconsistency
Indirectness
Imprecision
Publication bias
Large effect
Dose response
All plausible confounding & bias
• would reduce a demonstrated effect
or
• would suggest a spurious effect if no effect was observed
3.
Final level of confidence rating
Confidence in an estimate of effect across those considerations
High
⊕⊕⊕⊕
Moderate
⊕⊕⊕○
Low
⊕⊕○○
Very low
⊕○○○
2. Determinants of the Strength of Recommendation
Quality (certainty) of evidence
Balance between benefits, harms & burdens
Patients' values & preferences
Resources and cost
3. Implication of the Strength of Recommendation
Strong
❖ Population: Most people in this situation would want the recommended course of action and only a small proportion would not
❖ Health care workers: Most people should receive the recommended course of action
❖ Policy makers: The recommendation can be adapted as a policy in most situations
Weak
❖ Population: The majority of people in this situation would want the recommended course of action, but many would not
❖ Health care workers: Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision making
❖ Policy makers: There is a need for substantial debate and involvement of stakeholders

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology (unrestricted use of the figure granted by the US GRADE Network) (1,2).

2. We recommend against testing a removed *Ixodes* tick for *B. burgdorferi (strong recommendation, moderate-quality evidence)*. **Comment:** The presence or absence of *B. burgdorferi* in an *Ixodes* tick removed from a person does not reliably predict the likelihood of clinical infection.

B. Diagnostic testing of asymptomatic patients following tick bites

Recommendation:

1. We recommend against testing asymptomatic patients for exposure to *B. burgdorferi* following an *Ixodes* spp. tick bite *(strong recommendation, moderate-quality evidence).*

III. Who should receive antibiotic prophylaxis to prevent Lyme disease following presentation with a tick bite?

Recommendation:

1. We recommend that prophylactic antibiotic therapy be given only to adults and children within 72 hours of removal of an identified high-risk tick bite, but not for bites that are equivocal risk or low risk *(strong recommendation, high-quality evidence)*. **Comment**: If a tick bite cannot be classified with a high level of certainty as a high-risk bite, a wait-and-watch approach is recommended. A tick bite is considered to be high-risk only if it meets the following 3 criteria: the tick bite was from (a) an identified *Ixodes* spp. vector species, (b) it occurred in a highly endemic area, and (c) the tick was attached for ≥36 hours.

IV. What is the preferred antibiotic regimen for the chemoprophylaxis of Lyme disease following a high-risk tick bite?

Recommendation:

1. For high-risk *Ixodes* spp. bites in all age groups, we recommend the administration of a single dose of oral doxycycline within 72 hours of tick removal over observation *(strong recommendation, moderate-quality evidence)*. **Comment:** Doxycycline is given as a single oral dose, 200 mg for adults and 4.4 mg/kg (up to a maximum dose of 200 mg) for children.

V. What is the preferred diagnostic testing strategy for erythema migrans?

Recommendations:

1. In patients with potential tick exposure in a Lyme disease endemic area who have 1 or more skin lesions compatible with erythema migrans, we recommend clinical diagnosis rather than laboratory testing *(strong recommendation, moderate-quality evidence)*.
2. In patients with 1 or more skin lesions suggestive of, but atypical for erythema migrans, we suggest antibody testing performed on an acute-phase serum sample (followed by a convalescent-phase serum sample if the initial result is negative) rather than currently available direct detection methods such as polymerase chain reaction (PCR) or culture performed on blood or skin samples *(weak recommendation, low-quality evidence)*. **Comment:** If needed, the convalescent-phase serum sample should be collected at least 2–3 weeks after collection of the acute-phase serum sample.

VI. What are the preferred antibiotic regimens for the treatment of erythema migrans?

Recommendation:

1. For patients with erythema migrans, we recommend using oral antibiotic therapy with doxycycline, amoxicillin, or cefuroxime axetil *(strong recommendation; moderate-quality evidence)*. **Comment:** For patients unable to take both doxycycline and beta-lactam antibiotics, the preferred second-line agent is azithromycin.

VII. How long should a patient with erythema migrans be treated?

Recommendation:

1. We recommend that patients with erythema migrans be treated with either a 10-day course of doxycycline or a 14-day course of amoxicillin or cefuroxime axetil rather than longer treatment courses *(strong recommendation, moderate-quality evidence)*. **Comment:** If azithromycin is used, the indicated duration is 5–10 days, with a 7-day course preferred in the United States, as this duration of therapy was used in the largest clinical trial performed in the United States (3).

VIII. Should patients with the southern tick–associated rash illness (STARI) be treated with antibiotics?

Recommendation:

1. In patients who develop an erythema migrans–like skin lesion following the bite of the lone star tick (*Amblyomma americanum*), an illness referred to as STARI, we make no recommendation for or against the use of antibiotics *(no recommendation; knowledge gap)*. **Comment:** In certain geographic regions both STARI and Lyme disease are endemic (4). Distinguishing single erythema migrans due to Lyme disease from STARI may not be possible clinically unless the responsible tick has been identified (5). When STARI cannot be distinguished from Lyme disease–associated erythema migrans in areas endemic for both conditions, antibiotic therapy directed toward Lyme disease is indicated.

IX. What is the preferred diagnostic testing strategy for Lyme neuroborreliosis?

Recommendations:

1. When assessing patients for possible Lyme neuroborreliosis involving either the peripheral nervous system (PNS) or central nervous system (CNS), we recommend serum antibody testing rather than PCR or culture of either cerebrospinal fluid (CSF) or serum *(strong recommendation, moderate-quality evidence)*.

2. If CSF testing is performed in patients with suspected Lyme neuroborreliosis involving the CNS, we (a) recommend obtaining simultaneous samples of CSF and serum for determination of the CSF:serum antibody index, carried out by a laboratory using validated methodology, (b) recommend against CSF serology without measurement of the CSF:serum antibody index, and (c) recommend against routine PCR or culture of CSF or serum *(strong recommendation, moderate-quality evidence)*.

X. For which neurologic presentations should patients be tested for Lyme disease?

Recommendations:

1. In patients presenting with 1 or more of the following acute disorders: meningitis, painful radiculoneuritis, mononeuropathy multiplex including confluent mononeuropathy multiplex, acute cranial neuropathies (particularly VII, VIII, less commonly III, V, VI, and others), or in patients with evidence of spinal cord (or rarely brain) inflammation, the former particularly in association with painful radiculitis involving related spinal cord segments, and with epidemiologically plausible exposure to ticks infected with *B. burgdorferi*, we recommend testing for Lyme disease *(strong recommendation, moderate-quality evidence)*.
2. In patients with typical amyotrophic lateral sclerosis, relapsing-remitting multiple sclerosis, Parkinson's disease, dementia or cognitive decline, or new-onset seizures, we recommend against routine testing for Lyme disease *(strong recommendation, low-quality evidence)*.
3. In patients with neurologic syndromes other than those listed in [1] or [2], in the absence of a history of other clinical or epidemiologic support for the diagnosis of Lyme disease, we recommend against screening for Lyme disease *(strong recommendation, low-quality evidence)*.
4. In patients presenting with nonspecific magnetic resonance imaging white matter abnormalities confined to the brain in the absence of a history of other clinical or epidemiologic support for the diagnosis of Lyme disease, we suggest against testing for Lyme disease *(weak recommendation, low-quality evidence)*.

XI. Should adult patients with psychiatric illnesses be tested for Lyme disease?

Recommendation:

1. In patients with psychiatric illness, we recommend against routine testing for Lyme disease *(strong recommendation, low-quality evidence)*.

XII. Should children with developmental, behavioral, or psychiatric disorders be tested for Lyme disease?

Recommendation:

1. In children presenting with developmental, behavioral, or psychiatric disorders, we suggest against routinely testing for Lyme disease *(weak recommendation, low-quality evidence)*.

XIII. What are the preferred antibiotic regimens for the treatment of acute neurologic manifestations of Lyme disease without parenchymal involvement of the brain or spinal cord?

Recommendation:

1. In patients with Lyme disease–associated meningitis, cranial neuropathy, radiculoneuropathy, or with other PNS manifestations, we recommend using intravenous (IV) ceftriaxone, cefotaxime, penicillin G, or oral doxycycline over other antimicrobials *(strong recommendation, moderate-quality evidence)*. **Comment:** Decisions about the choice of antibiotic among these, including the route of administration, should primarily be made based on individual factors such as side effect profile, ease of administration, ability to tolerate oral medication, concerns about compliance unrelated to effectiveness. Treatment route may be changed from IV to oral during treatment. The preferred antibiotic duration is 14–21 days.

XIV. Should patients with Lyme disease–related parenchymal involvement of the brain or spinal cord be treated with oral or intravenous antibiotics?

Recommendation:

1. In patients with Lyme disease–associated parenchymal involvement of the brain or spinal cord, we recommend using IV over oral antibiotics *(strong recommendation, moderate-quality evidence)*.

XV. Should patients with Lyme disease and facial nerve palsy receive corticosteroids in addition to antimicrobial therapy?

Recommendation:

1. In patients with Lyme disease–associated facial nerve palsy, we make no recommendation on the use of corti-

costeroids in addition to antibiotics (no recommendation; knowledge gap). **Comment:** In patients age 16 or older presenting with acute facial nerve palsy but without other objective clinical or serologic evidence of Lyme disease, corticosteroid treatment should be administered within 72 hours in accordance with current facial nerve palsy guideline recommendations (6).

XVI. Should all patients with early Lyme disease receive an electrocardiogram (ECG) to screen for Lyme carditis?

Recommendation:

1. We suggest performing an ECG only in patients with signs or symptoms consistent with Lyme carditis *(weak recommendation, low-quality evidence)*. **Comment:** Symptoms and signs of cardiac involvement in Lyme disease include dyspnea, edema, palpitations, lightheadedness, chest pain, and syncope.

XVII. Which patients with Lyme carditis require hospitalization?

Recommendation:

1. In patients with or at risk for severe cardiac complications of Lyme disease including those with significant PR prolongation (PR >300 milliseconds), other arrhythmias, or clinical manifestations of myopericarditis, we recommend hospital admission with continuous ECG monitoring *(strong recommendation, very low-quality evidence).* **Comment:** Clinical manifestations of Lyme carditis include exercise intolerance, palpitations, presyncope, syncope, pericarditic pain, evidence of pericardial effusion, elevated biomarkers (such as troponin), edema, and shortness of breath.

XVIII. What pacing modality should be used if needed for the management of Lyme carditis?

Recommendation:

1. For patients with symptomatic bradycardia due to Lyme carditis that cannot be managed medically, we recommend temporary pacing modalities rather than implanting a permanent pacemaker *(strong recommendation, moderate-quality evidence)*.

XIX. What are the preferred antibiotic regimens for the treatment of Lyme carditis?

Recommendations:

1. In outpatients with Lyme carditis, we suggest oral antibiotics over IV antibiotics *(weak recommendation, very low-quality evidence)*.
2. In the hospitalized patient with Lyme carditis, we suggest initially using IV ceftriaxone over oral antibiotics until there is evidence of clinical improvement, then switching to oral antibiotics to complete treatment *(weak recommendation, very low-quality evidence)*.
3. For the treatment of Lyme carditis, we suggest 14–21 days of total antibiotic therapy over longer durations of treatment *(weak recommendation, very low-quality evidence)*. **Comment:** Oral antibiotic choices for Lyme carditis are doxycycline, amoxicillin, cefuroxime axetil, and azithromycin.

XX. Should patients being evaluated for acute myocarditis/pericarditis or chronic cardiomyopathy of unknown cause be tested for Lyme disease?

Recommendations:

1. In patients with acute myocarditis/pericarditis of unknown cause in an appropriate epidemiologic setting, we recommend testing for Lyme disease *(strong recommendation, low-quality evidence).*
2. In patients with chronic cardiomyopathy of unknown cause, we suggest against routine testing for Lyme disease *(weak recommendation, low-quality evidence)*.

XXI. What is the preferred diagnostic testing strategy for Lyme arthritis?

Recommendations:

1. When assessing possible Lyme arthritis, we recommend serum antibody testing over PCR or culture of blood or synovial fluid/ tissue *(strong recommendation, moderate-quality evidence)*.
2. In seropositive patients for whom the diagnosis of Lyme arthritis is being considered but treatment decisions require more definitive information, we recommend PCR applied to synovial fluid or tissue rather than *Borrelia* culture of those samples *(strong recommendation, moderate-quality evidence).*

XXII. What are the preferred antibiotic regimens for the initial treatment of Lyme arthritis?

Recommendation:

1. For patients with Lyme arthritis, we recommend using oral antibiotic therapy for 28 days *(strong recommendation, moderate-quality evidence)*.

XXIII. What are the approaches to patients in whom Lyme arthritis has not completely resolved?

Recommendations:

1. In patients with Lyme arthritis with partial response (mild residual joint swelling) after a first course of oral antibiotic, we make no recommendation for a second course of antibiotic versus observation *(no recommendation, knowledge gap)*. **Comment:** Consideration should be given to exclusion of other causes of joint swelling than Lyme arthritis, medication adherence, duration of arthritis prior to initial treatment, degree of synovial proliferation versus joint swelling, patient preferences, and cost. A second course of oral antibiotics for up to 1 month may be a reasonable alternative for patients in whom synovial proliferation is modest compared to joint swelling and for those who prefer repeating a course of oral antibiotics before considering IV therapy.
2. In patients with Lyme arthritis with no or minimal response (moderate to severe joint swelling with minimal reduction of the joint effusion) to an initial course of oral antibiotic, we suggest a 2–4-week course of IV ceftriaxone over a second course of oral antibiotics *(weak recommendation, low-quality evidence)*.

XXIV. How should post-antibiotic (previously termed antibiotic-refractory) Lyme arthritis be treated?

Recommendation:

1. In patients who have failed 1 course of oral antibiotics and 1 course of IV antibiotics, we suggest a referral to a rheumatologist or other trained specialist for consideration of the use of disease-modifying antirheumatic drugs, biologic agents, intraarticular steroids, or arthroscopic synovectomy *(weak recommendation, very low-quality evidence)*. **Comment:** Antibiotic therapy for longer than 8 weeks is not expected to provide additional benefit to patients with persistent arthritis if that treatment has included 1 course of IV therapy.

XXV. Should patients with persistent symptoms following standard treatment of Lyme disease receive additional antibiotics?

Recommendation:

1. For patients who have persistent or recurring nonspecific symptoms such as fatigue, pain, or cognitive impairment following recommended treatment for Lyme disease, but who lack objective evidence of reinfection or treatment failure, we recommend against additional antibiotic therapy *(strong recommendation, moderate-quality evidence)*. **Comment:** Evidence of persistent infection or treatment failure would include objective signs of disease activity, such as arthritis, meningitis, or neuropathy.

XXVI. What is the preferred antibiotic regimen for the treatment of borrelial lymphocytoma?

Recommendation:

1. In patients with borrelial lymphocytoma, we suggest oral antibiotic therapy for 14 days *(weak recommendation, low-quality evidence)*.

XXVII. What is the preferred antibiotic regimen for the treatment of acrodermatitis chronica atrophicans?

Recommendation:

1. In patients with acrodermatitis chronica atrophicans, we suggest oral antibiotic therapy for 21–28 days over shorter durations *(weak recommendation, low-quality evidence)*.

XXVIII. Under what circumstances should a patient with Lyme disease be evaluated for coinfection with *A. phagocytophilum* or *B. microti*?

Recommendation:

1. In patients with Lyme disease who have a high-grade fever or characteristic laboratory abnormalities, clinicians should assess for possible coinfection with *Anaplasma phagocytophilum* and/or *B. microti* infection in geographic regions where these infections are endemic *(good practice statement)*. **Comment:** Coinfection should be investigated in patients who have a persistent fever for >1 day while on antibiotic treatment for Lyme disease. If fever persists despite treatment with doxycycline, *B. microti* infection is an important consideration.

Characteristic laboratory abnormalities found in both anaplasmosis and babesiosis include thrombocytopenia, leukopenia, neutropenia, and/or anemia. Evidence of hemolysis, such as elevated indirect bilirubin level, anemia, and elevated lactate dehydrogenase, is particularly suggestive of babesiosis.

Supplementary data. Supplementary materials (in addition to the full guideline) are available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41562/abstract. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Conflict of interest statement. See the Methodology section in the full guideline (on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41562/abstract) for approach to conflict of interest (COI) by the IDSA/AAN/ACR COI review group. The following list is a reflection of what has been reported to the IDSA/AAN/ACR COI review group. To provide thorough transparency, the IDSA/AAN/ACR requires full disclosure of all relationships, regardless of relevancy to the guideline topic. The assessment of disclosed relationships for possible COI is based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. 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Dr. Zemel has served as an advisor for Novartis Promotional Speakers Bureau. No other disclosures relevant to this article were reported. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

ACKNOWLEDGMENTS

The expert panel expresses its gratitude for thoughtful reviews of an earlier version to the external reviewers. The panel thanks the IDSA, AAN, and ACR for supporting the guideline development process.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Lantos had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ARTHRITIS & RHEUMATOLOGY
DOI 10.1002/ART.39332
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SPECIAL ARTICLE

2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis

A European League Against Rheumatism/American College of Rheumatology/ Paediatric Rheumatology International Trials Organisation Collaborative Initiative

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This criteria set has been approved by the European League Against Rheumatism (EULAR) Executive Committee and the American College of Rheumatology (ACR) Board of Directors. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All EULAR/ACR-approved criteria sets are expected to undergo intermittent updates.

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This article is published simultaneously in the March 2016 issue of *Annals of the Rheumatic Diseases*.

Supported by the American College of Rheumatology, the European League Against Rheumatism, and the Paediatric Rheumatology International Trials Organisation.

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Objective. **To develop criteria for the classification of macrophage activation syndrome (MAS) in patients with systemic juvenile idiopathic arthritis (JIA).**

Methods. **A multistep process, based on a combination of expert consensus and analysis of real patient data, was conducted. A panel of 28 experts was first asked to classify 428 patient profiles as having or not having MAS, based on clinical and laboratory features at the time of disease onset. The 428 profiles comprised 161 patients with systemic JIA–associated MAS and 267 patients with a condition that could potentially be confused with MAS (active systemic JIA without evidence of MAS, or systemic infection). Next, the ability of candidate criteria to classify individual patients as having MAS or not having MAS was assessed by evaluating the agreement between the classification yielded using the criteria and the consensus classification of the experts. The final criteria were selected in a consensus conference.**

Results. **Experts achieved consensus on the classification of 391 of the 428 patient profiles (91.4%). A total of 982 candidate criteria were tested statistically. The 37 best-performing criteria and 8 criteria obtained from the literature were evaluated at the consensus conference. During the conference, 82% consensus among experts was reached on the final MAS classification criteria. In validation analyses, these criteria had a sensitivity of 0.73 and a specificity of 0.99. Agreement between the classification (MAS or not MAS) obtained using the criteria and the original diagnosis made by the treating physician was high ($\kappa = 0.76$).**

Conclusion. **We have developed a set of classification criteria for MAS complicating systemic JIA and provided preliminary evidence of its validity. Use of these criteria will potentially improve understanding of MAS in systemic JIA and enhance efforts to discover effective therapies, by ensuring appropriate patient enrollment in studies.**

Introduction

Macrophage activation syndrome (MAS) is the term used to describe a potentially life-threatening complication of systemic inflammatory disorders, which occurs most commonly in systemic juvenile idiopathic arthritis (JIA) and in its adult equivalent, adult-onset Still's disease (1–4), although its occurrence in patients with other autoimmune or autoinflammatory conditions, i.e., adult- and childhood-onset systemic lupus erythematosus (5,6), Kawasaki disease (7,8), and periodic fever syndromes (9,10), is being reported with increased frequency. MAS is characterized by an overwhelming inflammatory reaction due to an uncontrolled and dysfunctional immune response involving the continual activation and expansion of T lymphocytes and macrophages, which results in massive hypersecretion of proinflammatory cytokines (11,12).

Characteristic clinical features of MAS are high, nonremitting fever, hepatosplenomegaly, generalized lymphadenopathy, central nervous system dysfunction, and hemorrhagic manifestations. Typical laboratory abnormalities include pancytopenia, increased levels of ferritin, liver enzymes, lactate dehydrogenase, triglycerides, D-dimers, and soluble interleukin-2 (IL-2) receptor α (also known as soluble CD25 [sCD25]), and decreased fibrinogen levels. A typical histopathologic feature of MAS is the accumulation of well-differentiated macrophages exhibiting hemophagocytic activity in bone marrow biopsy specimens or aspirates (13). Although the prevalence of MAS among patients with systemic JIA has been estimated to be ~10%, recent reports suggest that subclinical MAS may occur in as many as 30-40% of patients with systemic JIA (14,15).

MAS can result in progressive multi-organ failure and eventually a fatal outcome if unrecognized. Recent studies indicate a mortality rate of 8% (16,17), making

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Submitted for publication April 2, 2015; accepted in revised form November 30, 2015.

timely diagnosis and prompt initiation of appropriate treatment imperative. However, early recognition of MAS is often challenging, given the lack of a single pathognomonic clinical or laboratory feature. Furthermore, histopathologic features of hemophagocytosis may not be present in the initial stages (18,19) and lack specificity for hemophagocytic syndromes (20). In addition, features of MAS may be difficult to distinguish from other conditions that may present with overlapping manifestations, such as flares of systemic JIA or systemic infections. Recently, a wide disparity in the frequency and severity of the classic clinical and laboratory features across patients has been described (16,17).

The difficulties in making the diagnosis of MAS and its clinical heterogeneity, together with the recent advances in its treatment and in understanding of its pathophysiology and underlying genetic defects (11,21–23), emphasize the need for accurate criteria to aid physicians in appropriately classifying patients as having MAS to facilitate enrollment into clinical studies. The recognition that the syndrome is clinically similar to hemophagocytic lymphohistiocytosis (HLH) has led some to recommend the use of the HLH-2004 diagnostic guidelines (24). An alternative approach is based on application of the preliminary diagnostic guidelines for MAS complicating systemic JIA (25). However, although both sets of guidelines have been utilized for detecting MAS in patients with systemic JIA, each has several limitations (26). The primary purpose of the international collaborative project described herein, conducted under the auspices of the European League Against Rheumatism, the American College of Rheumatology, and the Paediatric Rheumatology International Trials Organisation (PRINTO), was to develop a set of classification criteria for MAS complicating systemic JIA, based on a combination of expert consensus, available evidence from the medical literature, and analysis of real patient data.

Methods

A multistep process was used in developing the classification criteria and included the following phases: 1) a Delphi survey of international pediatric rheumatologists, aimed at identifying MAS features potentially suitable for inclusion in classification criteria (27); 2) large-scale data collection on patients with systemic JIA–associated MAS and patients with 2 other conditions that potentially could be confused with MAS; 3) a web-based procedure for ascertaining consensus among experts; 4) selection of candidate criteria through statistical analyses; 5) selection of final classification criteria in a consensus conference; and 6) cross-sectional validation of final classification criteria. Health professionals and patient/parent representatives were not included in the study task force because the project did not involve any issues of specific interest to these stakeholders. In particular, none of the study assessments required the participation of health professionals, and no patient/parent-reported outcomes were incorporated.

Data collection on patients with MAS and patients with conditions that could be confused with MAS. The design, inclusion criteria, and data collection procedures of this portion of the project have been described in detail previously (16,17,26). Briefly, international pediatric rheumatologists and pediatric hematologists were invited to participate in a retrospective cohort study of patients with systemic JIA–associated MAS or with 1 of 2 conditions that could potentially be confused with MAS, i.e., active systemic JIA not complicated by MAS and systemic infection.

For patients with MAS, information on laboratory features at 3 time points (the last visit before onset of MAS, the time of MAS onset, and the period of full-blown MAS) was collected. Because the classification criteria were aimed at identification of MAS in its earlier stages, only laboratory data recorded at the time of onset were retained. Data at the time of presentation in patients with conditions that could be confused with MAS were also obtained. Except for blood cell counts and acute-phase reactant levels, values of laboratory parameters were tested using both the original values provided by each local laboratory and the values standardized according to the SI unit system based on their normal ranges, as previously reported (16).

A total of 1,111 patients (362 with systemic JIA–associated MAS, 404 with active systemic JIA without MAS, and 345 with systemic infection) were reported by 95 pediatric subspecialists practicing in 33 countries in 6 continents. Pediatric subspecialists who provided these data are listed in Appendix A. The features of the patients with MAS and the comparison patients have been described elsewhere (16,17,26).

Web-based procedures for ascertaining consensus among experts. At present, there is no single feature that is pathognomonic for MAS. Furthermore, no prior validated diagnostic or classification criteria are available. In order to classify patients as having or not having MAS, we therefore decided to use expert consensus as the "gold standard." Based on publication records and experience in the care of children with MAS and related disorders, a panel of 28 experts (20 pediatric rheumatologists and 8 pediatric hematologists) was created.

The experts were asked to classify a total of 428 patient profiles as having or not having MAS, based on the clinical and laboratory features recorded at disease onset. The 428 profiles were selected randomly from among the 1,111 patients whose data were collected and comprised 161 patients with MAS, 140 patients with active systemic JIA without evidence of MAS, and 127 patients with systemic infection. Selection bias was unlikely, as the characteristics of patients who were selected and those who were not selected were comparable (data not shown). The experts were intentionally kept unaware of the original diagnosis and overall course of each patient.

Each patient profile included information about the presence or absence of key clinical manifestations, and the values of laboratory parameters and normal ranges at the respective institutions. Based on these data, all experts were asked to classify each patient as having or not having MAS. The minimum required level of agreement among experts was set at 80%. If an 80% consensus was not attained, the patient profile was discussed in a further round. Profiles for which consensus had not been achieved after the final round were declared

uninterpretable and discarded from further analyses. Three rounds of voting were used, with prior vote data and recorded comments available to all of the participants before each vote took place, to augment the number of consensus decisions. All web-based consensus procedures were conducted by PRINTO.

Selection of best classification criteria through statistical analyses. All statistical analyses used for selecting the best classification criteria were conducted only on the sample of patients for whom the experts achieved consensus about the diagnosis of MAS or non-MAS. Cutoff values for laboratory tests were calculated with the receiver operator characteristic (ROC) curve method, by identifying the point on the ROC curve that best discriminated between patients classified by the experts as having MAS and those classified as not having MAS.

The aim of this exercise was to assess the ability of candidate criteria to classify individual patients as having or not having MAS, and to evaluate the agreement between the classification yielded by the criteria and the consensus classification of experts. Candidate classification criteria were partly derived from the literature and partly generated from the study data.

Literature criteria included the following: 1) the preliminary diagnostic guidelines for MAS complicating systemic JIA (25), 2) the same guidelines modified by addition of the item ferritin at various threshold levels (500, 1,000 or 1,500 ng/ml), and 3) the HLH-2004 diagnostic guidelines (24), adapted by eliminating 3 of the 8 items because information about presence of hemophagocytosis was not available for both comparison groups, and neither natural killer (NK) cell activity nor sCD25 levels were determined in all patients. Criteria obtained from the study data were generated in 2 ways: 1) through the evaluation, by the project steering committee, of all combinations of clinical and laboratory variables (see some examples in Supplementary Table 1, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39332/abstract) (combination of criteria approach), and 2) by assigning weights to clinical and laboratory variables, on the basis of their association with the diagnosis of MAS made by the experts, through multivariable logistic regression analysis. For each combination of variables that were significantly associated with the diagnosis of MAS in logistic regression models, the rule was to convert the odds ratio of each variable to its percentage value out of a total of 100%. Each set of criteria was then composed of a group of variables whose sum of weights made up a total score of 100 (MAS score). The cutoff value in the MAS score that was associated with the higher likelihood of the presence of MAS was obtained by calculating the point on the ROC curve that corresponded to the highest sensitivity and specificity.

A total of 982 candidate classification criteria were tested. For each set of criteria, we calculated the sensitivity (ability of the criteria to identify a patient as having MAS who had been classified as having MAS according to the expert panel), the specificity (ability of the criteria to identify a patient as not having MAS who had been classified as not having MAS by the experts), the positive and negative predictive value, the area under the ROC curve (AUC), and the kappa value for agreement between the classification yielded by the criteria and the classification made by the experts. Although

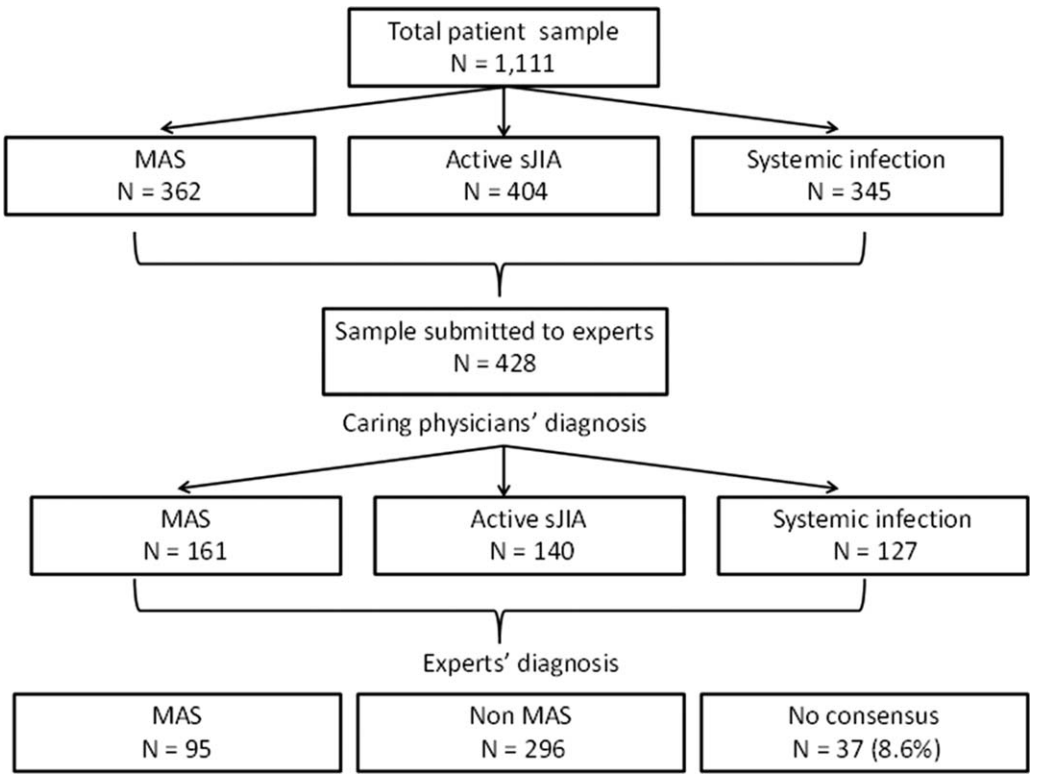

Figure 1. Patient samples evaluated in the study and results of web-based expert evaluations. MAS = macrophage activation syndrome; sJIA = systemic juvenile idiopathic arthritis.

there was one single model with the highest predictive value (criterion no. 929; Supplementary Table 1), we generated multiple combinations for comparison because we believed that less predictive models might have more face validity with the experts. Nevertheless, it was established that in order to qualify for inclusion in expert voting procedures at the consensus conference, a set of classification criteria should demonstrate a kappa value of ≥0.85, a sensitivity of ≥0.80, a specificity of ≥0.93, and an AUC of ≥0.90. An exception was made for the historical literature criteria, which were retained for further consideration even if they did not meet all statistical requirements.

Selection of the final classification criteria at consensus conference. The International Consensus Conference on MAS Classification Criteria was held in Genoa, Italy on March 21–22, 2014. The meeting was attended by all 28 experts who participated in web-based consensus evaluations and was facilitated by 2 moderators (HIB and NR) with expertise in nominal group technique. The overall goal of the meeting was to decide on a preliminary set of classification criteria using a combination of statistical and consensus formation techniques.

A plenary session was first held to present the scope, methodology, and flow of the project, the results of the Delphi survey, the characteristics of patients included in the data collection, the results of web-based consensus procedures and of statistical analyses of candidate classification criteria, and the methodology of the nominal group technique. Participants were then randomized into 2 equal-sized nominal groups and were asked to rank using nominal group technique, independently of each other and based on the evaluation of both ease of use and credibility (face/content validity) and statistical performance (particularly in terms of sensitivity, specificity, and kappa value), the 5 best classification criteria from 5 (highest) to 1 (lowest). All experts were connected by their laptops to a central computer and submitted all of their rankings electronically. A series of repeated independent voting sessions was held until the top 3 classification criteria were selected by each voting group. Then an 80% consensus was attained on the best (final) set of classification criteria, in a session with members of the 2 nominal groups combined.

Analysis of the association between the variables included in the final classification criteria and the web-based experts' consensus evaluations. The association between the final classification criteria and the web-based evaluations made by the experts was assessed by multiple logistic regression analysis, which used as explanatory variables the individual items included in the final classification criteria and as the dependent variable the web-based expert consensus on classification of patients as having or not having MAS. The effect was expressed in terms of odds ratios, and 95% confidence intervals were calculated; statistical significance was tested by likeli-

Table 1. Comparison of clinical and laboratory features at disease onset between patients classified by the 28-member expert panel as having macrophage activation syndrome (MAS) (n = 95) and those classified as not having MAS (n = 296)

	Patients classified as having MAS		Patients classified as not having MAS		
	No. with available data	No. (%) or median (IQR)*	No. with available data	No. (%) or median (IQR)*	*P*
Clinical manifestations					
Fever	94	93 (98.9)	294	278 (94.6)	0.08
Hepatomegaly	94	68 (72.3)	295	75 (25.4)	<0.0001
Splenomegaly	92	53 (57.6)	294	67 (22.8)	<0.0001
Lymphadenopathy	91	48 (52.8)	292	73 (25.0)	<0.0001
Central nervous system involvement	93	40 (43.0)	292	25 (8.6)	<0.0001
Hemorrhagic manifestations	92	25 (27.2)	294	16 (5.4)	<0.0001
Heart involvement	94	27 (28.7)	294	34 (11.6)	<0.0001
Lung involvement	95	27 (28.4)	294	40 (13.6)	0.0009
Kidney involvement	95	16 (16.8)	295	16 (5.4)	0.0004
Laboratory results					
Hemoglobin, gm/dl	95	9.9 (8.0–11.2)	289	10.9 (9.4–12.2)	<0.0001
White blood cell count, $\times 10^9$/liter	95	8.1 (3.2–12.8)	289	15.3 (9.9–20.1)	<0.0001
Neutrophil count, $\times 10^9$/liter	82	3.7 (1.5–8.0)	236	9.4 (5.1–14.2)	<0.0001
Platelet count, $\times 10^9$/liter	95	98 (57–141)	290	385 (286–551)	<0.0001
Erythrocyte sedimentation rate, mm/hour	90	28 (17–65)	245	70 (39–93)	<0.0001
C-reactive protein, mg/dl	85	8.7 (2.4–16.1)	282	8.2 (2.4–15.6)	0.63
Aspartate aminotransferase, units/liter	93	171 (98–436)	284	30 (22–45)	<0.0001
Alanine aminotransferase, units/liter	91	115 (43–283)	284	18 (12–34)	<0.0001
Lactate dehydrogenase, units/liter	81	1,560 (801–2,400)	248	482 (362–688)	<0.0001
Triglycerides, mg/dl	86	267 (192–358)	186	123 (96–160)	<0.0001
Albumin, gm/dl	79	3.0 (2.6–3.5)	252	3.7 (3.2–4.1)	<0.0001
Serum sodium, mEq/liter	80	136 (133–140)	259	138 (136–141)	0.003
Fibrinogen, mg/dl	88	220 (148–345)	226	500 (356–650)	<0.0001
Ferritin, ng/ml	90	9,094 (2,000–19,767)	244	268 (62–938)	<0.0001
D-dimer, ng/ml	48	3,579 (1,834–7,373)	94	1,638 (528–3,325)	<0.0001

* Clinical manifestations are reported as the number (%) and laboratory results as the median (interquartile range [IQR]).

Table 2. Univariate analysis of the ability of specific variables to distinguish patients with macrophage activation syndrome from comparison patients, as assessed using the 391 patients for whom expert consensus was achieved

	No. of patients with available data	OR (95% CI)*	*P*
Clinical features			
Central nervous system involvement	385	8.1 (4.5–14.4)	<0.0001
Hepatomegaly	389	7.7 (4.5–12.9)	<0.0001
Hemorrhagic manifestations	386	6.5 (3.3–12.8)	<0.0001
Fever	388	5.4 (0.7–40.9)	0.106
Splenomegaly	386	4.6 (2.8–7.6)	<0.0001
Lymphoadenopathy	383	3.4 (2.1–5.5)	<0.0001
Kidney involvement	390	3.5 (1.7–7.4)	0.0008
Heart involvement	388	3.1 (1.7–5.5)	0.0001
Lung involvement	389	2.5 (1.4–4.4)	0.0011
Active arthritis	390	1.6 (1.0–2.6)	0.0587
Laboratory features			
Non-normalized values			
Ferritin >684 ng/ml	334	111.6 (26.7–465.8)	<0.0001
Platelet count ≤181 × 10^9/liter	385	84.3 (40–177.5)	<0.0001
Aspartate aminotransferase >48 units/liter	377	51.9 (21.7–124.4)	<0.0001
Lactate dehydrogenase >853 units/liter	329	20.0 (10.7–37.3)	<0.0001
Triglycerides >156 mg/dl	272	19.6 (9.4–40.8)	<0.0001
Alanine aminotransferase >36 units/liter	375	18.0 (9.4–34.3)	<0.0001
Fibrinogen ≤360 mg/dl	314	11.5 (6.3–21.0)	<0.0001
Neutrophil count ≤3.7 × 10^9/liter	318	5.9 (3.4–10.5)	<0.0001
D-dimer >1,350 ng/ml	142	5.7 (2.4–13.4)	<0.0001
Erythrocyte sedimentation rate ≤30 mm/hour	335	5.6 (3.3–9.5)	<0.0001
Albumin ≤3.6 gm/dl	331	5.5 (3.0–10.1)	<0.0001
Hemoglobin ≤8.5 gm/dl	384	4.9 (2.7–8.8)	<0.0001
White blood cell count ≤10.2 × 10^9/liter	384	4.6 (2.8–7.5)	<0.0001
Serum sodium ≤133, mEq/liter	339	2.9 (1.7–5.0)	0.0002
C-reactive protein >0.86 mg/dl	367	2.4 (1.0–5.9)	0.0501
Normalized values			
Ferritin >2,773.6 ng/ml	334	23.9 (12.7–44.8)	<0.0001
Aspartate aminotransferase >44.4 units/liter	377	47.4 (21.6–103.9)	<0.0001
Alanine aminotransferase >23 units/liter	375	39.4 (14.1–110.5)	<0.0001
Lactate dehydrogenase >238.8 units/liter	329	39.2 (18.2–84.6)	<0.0001
Triglycerides >193.9 mg/dl	272	16.3 (8.7–30.8)	<0.0001
Fibrinogen ≤318.9 mg/dl	314	11.0 (6.1–20.0)	<0.0001
Albumin ≤3.9 gm/dl	331	6.4 (3.6–11.3)	<0.0001
D-dimer >1,320.3 ng/ml	142	5.2 (2.1–12.7)	<0.0001
Serum sodium ≤135 mEq/liter	339	3.3 (1.9–5.6)	<0.0001

* OR = odds ratio; 95% CI = 95% confidence interval.

hood ratio test. The AUC of the model was used as an indicator of its predictive ability. The purpose of this post-consensus analysis was to evaluate which were the variables that most influenced the experts' decision to classify the patients as having or not having MAS.

Validation of final classification criteria. Validation analysis was performed by assessing the performance of the criteria, in terms of sensitivity, specificity, negative predictive value, positive predictive value, AUC, and kappa value, in discriminating patients with MAS from patients with the 2 conditions with which MAS could be confused (combined in a single group), using the original diagnosis made by the caring physician (i.e., the investigator who entered the patient's data in the study web site) as the gold standard. This analysis was performed on the sample of patients not used for expert evaluations (n = 683). Only patients with available data on all items included in the final classification criteria were used for the analyses.

Results

Results of web-based process for ascertainment of expert consensus. After 3 rounds of web-based evaluations, the experts achieved consensus on the classification of 391 (91.4%) of the 428 patient profiles examined (Figure 1). A total of 95 patients were classified as having MAS by the experts, 88 of whom had also been diagnosed as having MAS by the treating physician; the original diagnosis had been systemic JIA without MAS in 3 patients and systemic infection in 4. A total of 296 patients were classified by the experts as not having MAS, 47 of whom had been diagnosed as having MAS by the treating physician. Thirty-seven patient profiles for which 80% consensus among experts was not reached were discarded. A comparison of

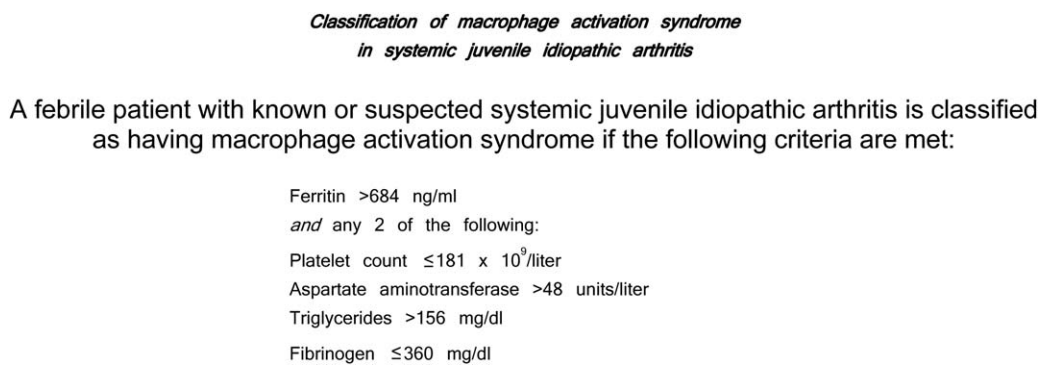
Classification of macrophage activation syndrome
in systemic juvenile idiopathic arthritis
A febrile patient with known or suspected systemic juvenile idiopathic arthritis is classified as having macrophage activation syndrome if the following criteria are met:
Ferritin >684 ng/ml
and any 2 of the following:
Platelet count ≤181 x 10^9/liter
Aspartate aminotransferase >48 units/liter
Triglycerides >156 mg/dl
Fibrinogen ≤360 mg/dl

Figure 2. Criteria for the classification of macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. Laboratory abnormalities should not be otherwise explained by the patient's condition, such as concomitant immune-mediated thrombocytopenia, infectious hepatitis, visceral leishmaniasis, or familial hyperlipidemia.

clinical and laboratory features between patients diagnosed by the experts as having MAS and those diagnosed as not having MAS is shown in Table 1. Overall, patients whose condition was classified as MAS by the experts had more severe clinical and laboratory features than those classified as not having MAS.

Candidate clinical and laboratory variables determined by univariate analysis. In univariate analyses, the 10 variables found to have the greatest ability to distinguish patients with MAS from comparison patients were as follows: ferritin level, platelet count, levels of aspartate transaminase (AST), lactate dehydrogenase, triglycerides, alanine transaminase (ALT), and fibrinogen, central nervous system involvement, hepatomegaly, and hemorrhagic manifestations (Table 2). These variables qualified for inclusion in logistic regression analyses aimed at generating candidate classification criteria through the MAS score method described above. However, ALT levels were excluded owing to their close correlation with AST levels and a slightly lower statistical performance. They were replaced by neutrophil count or albumin level, depending on the model.

Table 3. Logistic regression model to assess association between the variables included in the final classification criteria and the experts' consensus of patients' classification as having or not having macrophage activation syndrome*

Explanatory variable	OR (95% CI)	*P*†
Ferritin >684 ng/ml	>999.999 (40.6−>999.999)	<0.0001
Platelet count ≤181 × 10^9/liter	237.0 (18.2−>999.999)	<0.0001
Triglycerides >156 mg/dl	18.3 (2.0–163.9)	0.009
Fibrinogen ≤360 mg/dl	16.0 (2.0–126.4)	0.009
Aspartate aminotransferase >48 units/liter	10.0 (1.3–78.4)	0.029

* The experts' consensus on patients' classification as having or not having macrophage activation syndrome (from the web-based process) was the dependent variable. Complete data were available on 227 patients. The area under the receiver operating characteristic curve of the model was 0.99. OR = odds ratio; 95% CI = 95% confidence interval.
† By likelihood ratio test.

Candidate classification criteria sets. Of the 982 sets of criteria tested, 45 were retained for further evaluation at the consensus conference. Of these, 37 (20 generated through the combination of criteria approach and 17 obtained with the MAS score method) were represented by criteria that met the statistical requirements described in Methods, and 8 were criteria derived from the literature. The statistical performance of the 20 best candidate criteria is presented in Supplementary Table 1 (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39332/abstract). The definition of and statistics on all 982 criteria tested are available from the corresponding author upon request.

Final classification criteria selected at face-to-face conference. During the consensus conference, 7 voting sessions were held among the 28 experts until 3 top classification criteria sets remained (criteria nos. 466, 472, and 929; Supplementary Table 1). Notably, the same criteria were selected independently by the 2 nominal groups, confirming convergent validity of the selection process. After the last voting session, 82% consensus was reached on the final definition (criteria no. 472; Supplementary Table 1). A subsequent open face-to-face discussion among all experts led to the decision to include in the final definition the presence of fever as a mandatory criterion and the requirement that the patient should have known or suspected systemic JIA. The final classification criteria selected at the consensus conference are presented in Figure 2.

Association between final classification criteria and experts' web-based consensus evaluations. For this multivariable analysis, complete data were available on 227 patients. The logistic regression model to evaluate

which were the variables included in the final classification criteria that most influenced the experts' decision to classify a patient as having or not having MAS is presented in Table 3. All variables were independently correlated with the experts' diagnoses. However, the association was much stronger for ferritin and platelet count. The AUC of the model was 0.99.

Preliminary validation of the final criteria set. The evaluation of the ability of the new classification criteria to discriminate MAS from comparator conditions in the patient sample not included in the expert evaluations (n = 415 of 683) showed a sensitivity of 0.73, a specificity of 0.99, a positive predictive value of 97.4%, a negative predictive value of 85.9%, an AUC of 0.86, and a kappa value for agreement between the diagnosis yielded by the criteria and the diagnosis made by the treating physician of 0.76.

Discussion

Using a consensus process as well as a statistical approach, we have developed a new set of classification criteria for MAS complicating systemic JIA (Figure 2). Because the criteria were established against comparison samples composed of patients with either a rheumatologic condition (active systemic JIA without evidence of MAS) or a nonrheumatologic condition (systemic infection), they may be of interest to a specialists in a range of disciplines.

The classification criteria include only laboratory variables and no clinical manifestations, with the exception of fever. This choice is in accordance with the common view that suspicion of MAS is most commonly raised by detection of subtle laboratory alterations, whereas clinical symptoms are often delayed and/or similar to those observed in other conditions (28). In a previous analysis of the MAS sample included in the present study, we found that 4 of the 5 laboratory tests that are part of the criteria (ferritin, platelet count, AST, and triglycerides) were among the parameters that showed a change of >50% between the last visit before the onset of MAS and the onset of MAS (16). In the same study, ferritin levels exhibited the largest change over time, which underscores the major importance of this feature in MAS detection and supports its use as a mandatory criterion. The key value of ferritin in the classification of MAS was corroborated by the observation that it was the parameter that had the greatest influence on the experts' classification of patients as having or not having MAS (Table 3).

Although the presence of fever did not enable discrimination between MAS and comparator illnesses as it was found in all or nearly all patients in each sample, the expert panel considered fever a prerequisite for the classification of MAS. The cardinal diagnostic role of fever is substantiated by the observation that it was the mostly highly ranked clinical feature identified in the Delphi survey (27). Unfortunately, we lacked reliable information on the pattern of fever in the 3 patient groups. However, it is generally accepted that the onset of MAS is heralded by a shift from the high-spiking intermittent pattern typical of active systemic JIA to a continuous nonremitting pattern (3,4,29).

The detection of macrophage hemophagocytosis in bone marrow biopsy specimens or aspirates or reticuloendothelial organ biopsy specimens is another frequent and characteristic feature of MAS. However, because hemophagocytosis is often absent during the early stages of MAS (18,19) and its demonstration requires an invasive procedure, the expert panel deemed it not necessary for the classification of systemic JIA–associated MAS. Notably, the demonstration of hemophagocytosis is not mandatory in either the HLH-2004 or the preliminary MAS diagnostic guidelines (24,25).

Although possibly useful for diagnostic purposes, the classification criteria are primarily intended for use in clinical trials and research studies. The criteria exhibited high accuracy and face/content validity in consensus and statistical evaluations, but it should be taken into account that they were developed using expert consensus as the gold standard. It also should be noted that the experts were asked to differentiate MAS from non-MAS conditions by reviewing the clinical features and laboratory values recorded at a single point in time (i.e., at disease onset), and were unaware of the patient's clinical course, laboratory values over time, response to treatment, or outcome. This information was, however, available to the treating physician, who made the original diagnosis in the clinical setting. This disparity in the available information may partially explain the high proportion of patients who were diagnosed by the treating physician as having MAS but classified by the experts as not having MAS (47 of 161; 29.2%). It is conceivable that because the experts were provided with only the information relevant to the development of the criteria, they tended to confirm the diagnosis of MAS only in straightforward and unambiguous cases.

It is therefore important to emphasize that the classification criteria may not capture all instances of MAS seen in the routine clinical setting, particularly those with subtle onset or incomplete clinical expression. Notably, of the 47 patients for whom the treating physician's diagnosis of MAS was not confirmed by the experts, 30 (63.8%) also did not meet the final classification criteria, 11 (23.4%) could not be assessed due to lack of data on the laboratory variables needed to apply the criteria, and only 6 (12.8%)

were classified as having MAS according to the final classification criteria. In addition, only 18 (46.6%) of the 37 patients for whom the experts could not agree on the diagnosis were classified as having MAS according to the final classification criteria. These findings underscore the consistency of the experts' evaluations and support the validity of the final classification criteria.

The fact that the cutoff values for platelet count and fibrinogen level included in the criteria are within the normal range of routine laboratory assessments may be regarded as clinically implausible. The same may apply to the cutoffs for AST and triglycerides, which are only slightly above the upper limits of normal. However, it is widely recognized that children with active systemic JIA often have increased platelet counts (e.g., $>600 - 800 \times 10^9$/liter) as well as elevated fibrinogen levels (e.g., >500–600 mg/dl) as part of the underlying inflammatory process (30,31). Thus, a paradoxically normal platelet count or fibrinogen level in the setting of otherwise prominent systemic inflammation may raise the suspicion of MAS (16,28). Because the levels of serum transaminases and triglycerides are generally normal in children with systemic JIA who do not have other coexistent pathologic conditions (e.g., infectious hepatitis or familial hyperlipidemia), their simple increase above the upper normal limits, combined with the other clinical and laboratory parameters included in the criteria, may be sufficient to herald the occurrence of MAS. This fits with the real-world patient data used in these studies to establish cutoff values that distinguish between children with JIA who have MAS and those who do not have MAS.

A secondary objective of the present project was analysis of the role of change in laboratory findings over time in the detection of MAS. However, this exercise was performed only for descriptive purposes, i.e., to identify and rank the laboratory parameters for which change over time was deemed by the experts as most important or useful for early detection of MAS. Because serial laboratory results were available for patients with MAS but not for the comparator groups, we could not establish the threshold level of change in each parameter that had the greatest sensitivity and specificity for the diagnosis of MAS. This precluded the ability to incorporate the change in laboratory values over time in the classification criteria. Due to space constraints, this analysis is reported in a separate manuscript (32).

Recently there have been several reports, from randomized controlled clinical trials and from postmarketing experience, of MAS occurring in patients with systemic JIA being treated with the cytokine blockers canakinumab and tocilizumab (33–35). Because these agents inhibit the biologic effects of IL-1 and IL-6, respectively, which are among the proinflammatory cytokines involved in the physiopathology of MAS (11,36), it is conceivable that MAS episodes developing during treatment with these biologic agents may occur in the absence of fever or some of the typical laboratory abnormalities of the syndrome. Clinical symptoms in patients with systemic JIA–associated MAS receiving tocilizumab were found to be milder than those in patients not receiving this treatment (37). Preliminary analyses in patients who developed MAS while receiving tocilizumab or canakinumab have shown that a few cases did not meet the new criteria, due to the absence of fever or a peak ferritin level of <684 ng/ml (38,39). More data from real-world clinical practice are needed to establish whether the criteria should be refined to increase their power to identify MAS occurring during treatment with IL-1 and IL-6 inhibitors.

Our study should be interpreted in light of some potential caveats. Patient data were collected through retrospective review of clinical charts, and retrospective analysis is subject to missing and possibly erroneous data. However, because all patient profiles were reviewed by the experts and the diagnosis of MAS or non-MAS was confirmed only when a high level of consensus was reached, the impact of this potential limitation was likely minimized. Some important diagnostic parameters of MAS, such as sCD25 and sCD163 levels and NK cell activity, could not be assessed due to their unavailability in some of the patient samples. However, these biomarkers are not routinely assessed, nor are they timely, in most pediatric rheumatology centers.

In summary, we have developed a set of classification criteria for MAS complicating systemic JIA and provided preliminary evidence of their validity. These criteria will help standardize the design and conduct of future clinical trials and research studies and contribute to enhancing knowledge and awareness of the syndrome.

ACKNOWLEDGMENTS

The authors thank the PRINTO employees, Simona Angioloni, Chiara Pallotti, Michele Pesce, Mariangela Rinaldi, and Luca Villa, for technical assistance during the study and for technical and secretarial assistance in the organization of the consensus conference.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ravelli had full access to all of

the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ravelli, Minoia, Davì, Horne, Martini, Ruperto, Cron.

Acquisition of data. Ravelli, Minoia, Davì, Horne, Aricò, Avcin, Behrens, De Benedetti, Filipovic, Grom, Henter, Ilowite, Jordan, Khubchandani, Kitoh, Lehmberg, Lovell, Miettunen, Nichols, Ozen, Pachlopnik Schmid, Ramanan, Russo, Schneider, Sterba, Uziel, Wallace, Wouters, Wulffraat, Demirkaya, Brunner, Martini, Ruperto, Cron.

Analysis and interpretation of data. Ravelli, Minoia, Horne, Bovis, Pistorio, Brunner, Ruperto, Cron.

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EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors

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Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2020-217139).

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Received 10 February 2020
Revised 3 April 2020
Accepted 7 April 2020
Published Online First 23 April 2020

Check for updates

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To cite: Kostine M, Finckh A, Bingham 3rd CO, *et al*. *Ann Rheum Dis* 2021;**80**:36–48.

ABSTRACT

Background Rheumatic and musculoskeletal immune-related adverse events (irAEs) are observed in about 10% of patients with cancer receiving checkpoint inhibitors (CPIs). Given the recent emergence of these events and the lack of guidance for rheumatologists addressing them, a European League Against Rheumatism task force was convened to harmonise expert opinion regarding their identification and management.

Methods First, the group formulated research questions for a systematic literature review. Then, based on literature and using a consensus procedure, 4 overarching principles and 10 points to consider were developed.

Results The overarching principles defined the role of rheumatologists in the management of irAEs, highlighting the shared decision-making process between patients, oncologists and rheumatologists. The points to consider inform rheumatologists on the wide spectrum of musculoskeletal irAEs, not fulfilling usual classification criteria of rheumatic diseases, and their differential diagnoses. Early referral and facilitated access to rheumatologist are recommended, to document the target organ inflammation. Regarding therapeutic, three treatment escalations were defined: (1) local/systemic glucocorticoids if symptoms are not controlled by symptomatic treatment, then tapered to the lowest efficient dose, (2) conventional synthetic disease-modifying antirheumatic drugs, in case of inadequate response to glucocorticoids or for steroid sparing and (3) biological disease-modifying antirheumatic drugs, for severe or refractory irAEs. A warning has been made on severe myositis, a life-threatening situation, requiring high dose of glucocorticoids and close monitoring. For patients with pre-existing rheumatic disease, baseline immunosuppressive regimen should be kept at the lowest efficient dose before starting immunotherapies.

Conclusion These statements provide guidance on diagnosis and management of rheumatic irAEs and aim to support future international collaborations.

INTRODUCTION

Although the concept of immunotherapy in cancer is far from new, monoclonal antibodies targeting immunological checkpoints or 'checkpoint inhibitors' (CPIs) represent a growing class of agents across multiple tumour types and at all stages of disease. Agents targeting the T-cell cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or the programmed cell death-(ligand) 1 (PD-1/PD-L1) coinhibitory receptors marked a turning point in the success of immunotherapeutic approaches.[1–3] By enhancing antitumour T-cell activity, unprecedented long-lasting tumour responses were observed in patients with unresectable or advanced metastatic disease.[4–7] The clinical value of these immune CPIs, as single agents or in combination, is being investigated in various solid tumours and haematological malignancies, and their use is expanding rapidly.[8] So far, the Food and Drug Administration and the European Medicines Agency approved seven immune checkpoint-blocking antibodies in selected cancers: one anti-CTLA-4 (ipilimumab), three anti-PD-1 (nivolumab, pembrolizumab and cemiplimab) and three anti-PD-L1 (atezolizumab, avelumab and durvalumab).

The T-cell activation induced by CPIs commonly promotes inflammatory or autoimmune-like side effects, known as immune-related adverse events (irAEs).[9] Compared with conventional cancer therapies, this spectrum of toxicities is unique and can affect any organ system, most frequently the skin, gastrointestinal tract, endocrine glands and lung. Among irAEs, specific rheumatic manifestations have been described rather rarely in randomised clinical trials, but are much more common in clinical practice. The clinical features of rheumatic irAEs have been described in a growing number of case series and reports.[10] However, despite the growing interest for irAEs among rheumatologists, evidence is lacking for the optimal diagnostic approach and the management of these patients in ways that also permit effective antitumour therapy to continue. According to a recent survey, a large proportion of

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rheumatologists have limited experience and little confidence in managing rheumatic irAEs, highlighting the need for education and recommendations in this emerging condition.[11]

In 2017, the European Society for Medical Oncology developed clinical guidelines for the management of immune toxicities and mentioned the paucity of literature on management of rheumatic irAEs.[12] Three other consensus recommendations have been proposed by the Society for Immunotherapy of Cancer, the American Society of Clinical Oncology and The National Comprehensive Cancer Network, which among others included the management of inflammatory arthritis, polymyalgia rheumatica and myositis.[13–15] This European League Against Rheumatism initiative assembled international experts primarily from the rheumatology and immunology but also the oncology field with the explicit goal of generating the first set of recommendations for the diagnosis and the management of rheumatic irAEs arising as a direct consequence of CPI. Rheumatologists, but also in some countries internists and immunologists, have to play a pivotal role in developing with the oncologists a patient-centred approach to improve the management of rheumatic irAEs. While the initiative primarily set out to guide clinicians, it is noteworthy that there is limited and rapidly changing literature and that future additional studies can drastically change the profile for diagnosis and management. This area will be a continually evolving field; therefore, the accompanying comments may also serve as a framework for future longitudinal cohorts and/or clinical studies.

METHODS

After approval by the European League Against Rheumatism Executive Committee, an international task force was convened to develop points to consider for the diagnosis and the management of rheumatic irAEs due to cancer immunotherapy. Among these members, were 19 clinical experts from Europe and North America (14 rheumatologists including 2 delegates of the European League Against Rheumatism young rheumatologists' network EMEUNET, 2 internists and 3 oncologists), 1 clinical epidemiologist, 1 allied health professional and 2 patient representatives from the PARE network of patient research partners. The process adhered to the updated European League Against Rheumatism standardised operating procedures for the development of recommendations.[16]

In July 2018, the first meeting was convened in Zürich, Switzerland, to define the focus of the task force, identify the target population and the research questions for the systematic literature review (SLR). The SLR was performed by the research fellow (MK), with support from the clinical epidemiologist (AF) and a librarian (Catherine Weill), to identify relevant publications through December 2018. Based on the findings of the SLR, a first draft of points to consider including 12 items was prepared by the fellow (MK) and the two convenors (TS and XM).

SLR results were presented at a second meeting that was held in Zürich, Switzerland, in January 2019. Following the evaluation of literature and a group discussion of the first draft of propositions, the task force formulated overarching principles and consensus statements. Each proposal was then submitted to a voting process, requiring at least 75% of votes in the first ballot for each recommendation to be accepted. In case this threshold was not achieved, further discussion and textual changes were proposed for a second round, for which a 67% majority was required. Five members of the task force could not attend this second meeting, but they subsequently commented and voted on each statement by email. The level of evidence (LoE) and grade of recommendation was based on the Oxford Levels of Evidence.[17] After this second face-to-face meeting, members of the task force were asked to anonymously rate each item in an online survey, on a scale of 0 (absolutely disagree) to 10 (absolutely agree) to assess the level of agreement (LoA). Furthermore, the task force agreed on adding relevant references published between the SLR and the writing of this manuscript. The manuscript was reviewed and approved by all task force members and the European League Against Rheumatism Executive Committee before submission.

RESULTS

Systematic literature review

The literature search strategy and summary of results are detailed in online supplementary data. The first objective was to identify phase III clinical trials to assess the frequency and type of rheumatic and musculoskeletal diseases' (RMDs) complaints associated with CPI compared with the comparator group. The search was performed using Medline, Embase and the Cochrane Library, through December 2018. Among 630 references identified, 22 studies were selected for inclusion. The second objective was to obtain detailed information on rheumatic and musculoskeletal symptoms that have been described under CPI treatment. The third objective was to assess outcomes in patients with pre-existing autoimmune diseases. Therefore, relevant keywords relative to three key domains were used in Medline and Embase databases: immune CPIs, rheumatic and systemic diseases and adverse events. Abstracts from the last two European League Against Rheumatism and American College of Radiology meetings were included, combined with manual searches from references of the selected articles. From among 2156 references identified, 170 were included, including pharmacovigilance registries (n=5), case series (n=51) and case reports (n=114).

After group discussion of the results of the SLR, the consensus process was initiated and the full task force agreed on a final set of 4 overarching principles and 10 points to consider (table 1).

Overarching principles

A. Rheumatic and musculoskeletal immune-related adverse events can occur as manifestations in cancer patients receiving immunotherapy with checkpoint inhibitors (LoE na; LoA 9.6).

Analysis of phase III clinical trials revealed that arthralgia, arthritis, myalgia, myositis, dry mouth, musculoskeletal and back pain were reported in patients receiving CPI. However, their frequency was not significantly different to that of patients receiving chemotherapy or placebo.[5 18–38] Data from several series, both retrospective and prospective, reporting prevalences of rheumatic irAEs in real life, ranging from 1.5% to 22%, suggest that rheumatic irAEs are under-reported in clinical trials.[39–54] Of note, an heterogeneous definition of rheumatic irAEs may explain such wide interval. Many clinical trials do not report rheumatic irAEs (by disregarding of musculoskeletal/rheumatic events as a distinct organ system, even in the online supplementary data) or partially only report high-grade and/or frequent adverse events (ie, occurring in ≥10% of the patients). Therefore, the task force wanted to emphasise with this first principle that rheumatic and musculoskeletal manifestations are a relevant part of the broad spectrum of irAEs.

B. Management of rheumatic and musculoskeletal immune-related adverse events should be based on a shared decision-making process between patients, oncologists and rheumatologists (LoE na; LoA 9.5).

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Table 1 Overarching principles and points to consider for the diagnosis and management of rheumatic irAEs

		LoE	GoR	LoA (0–10) mean (SD)
Overarching principles				
A.	Rheumatic and musculoskeletal immune-related adverse events can occur as manifestations in cancer patients receiving immunotherapy with checkpoint inhibitors.	n.a.	n.a.	9.6 (0.7)
B.	Management of rheumatic and musculoskeletal immune-related adverse events should be based on a shared decision-making process between patients, oncologists and rheumatologists.	n.a.	n.a.	9.5 (1.1)
C.	Rheumatologists should engage with oncologists to contribute to the inter-disciplinary care of patients presenting with musculoskeletal signs and symptoms.	n.a.	n.a.	9.1 (1.2)
D.	The role of rheumatologists is to assist oncologists in differential diagnosis and to relieve rheumatic and musculoskeletal symptoms to an acceptable level enabling patients to maintain effective cancer immunotherapy.	n.a.	n.a.	9.5 (0.9)
Points to consider				
1.	Rheumatologists should be aware of the wide spectrum of clinical presentations of rheumatic and/or systemic immune-related adverse events that often do not fulfil traditional classification criteria of RMDs.	4	C	9.5 (1.2)
2.	Oncologists should be encouraged to consult rheumatologists promptly for assessment when rheumatic musculoskeletal and systemic signs or symptoms are suspected due to immunotherapy, and rheumatologists should provide facilitated access for such patients.	5	D	9.4 (1.3)
3.	Metastases, paraneoplastic syndromes and unrelated rheumatic diseases should be considered as a potential differential diagnosis of rheumatic immune-related events. The comprehensive assessment should be focused on documenting evidence of target organ inflammation, and based on history, clinical features, laboratory tests, imaging and/or biopsy.	4	C	9.5 (0.9)
4.	In case of inefficacy of symptomatic treatment and depending on the disease severity, local and/or systemic glucocorticoids should be considered for immune-related rheumatic and systemic symptoms. Dose regimen and route of administration should be decided according to the clinical entity and activity. When improvement is achieved, systemic glucocorticoids should be tapered to the lowest effective dose to control the symptoms.	4	C	9.4 (1)
5.	csDMARD should be considered in patients with insufficient response to acceptable dose of glucocorticoids or requiring glucocorticoid-sparing.	4	C	9 (1.2)
6.	For patients experiencing severe immune-related rheumatic and systemic immune-related adverse events or with insufficient response to csDMARD, bDMARD may be considered, with TNF or IL-6 inhibitors being the preferred options for inflammatory arthritis.	4	C	8.8 (1.2)
7.	The decision to hold or to continue the cancer immunotherapy should be based on the severity of rheumatic immune-related adverse events, the extent of required immunosuppressive regimen, the tumour response and its duration, as well as the future oncology treatment plan, in a shared decision with the patient.	5	D	9.4 (1)
8.	Myositis may be a severe condition. Immunotherapy withdrawal needs to be discussed. In the presence of life-threatening manifestations (bulbar symptoms (dysphagia, dysarthria, dysphonia), dyspnoea and myocarditis), high dose of glucocorticoids, IVIg and/or plasma exchange should be considered; immunotherapy withdrawal is always necessary.	4	C	8.9 (1.2)
9.	A pre-existing autoimmune rheumatic and/or systemic disease should not preclude the use of cancer immunotherapy. Baseline immunosuppressive regimen should be kept at the lowest dose possible (for glucocorticoids, below 10 mg prednisone per day if possible). However, many patients may have a flare of the underlying condition and/or immune-related adverse events, requiring the use of glucocorticoids and/or DMARDs.	4	C	9 (1.3)
10.	Before initiation of cancer immunotherapy, there is no indication to test every patient for the presence of autoantibodies. In the case of unexplained rheumatic, musculoskeletal or systemic symptoms, a complete rheumatological assessment should be performed.	5	D	9 (1.3)

GoR: A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level.
LoE: 1a: systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case–control studies; 3b: individual case–control study; 4: case-series (and poor quality cohort and case–control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.
bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; GoR, grade of recommendation; IL-6, interleukin 6; irAEs, immune-related adverse events; IVIg, intravenous immunoglobulin; LoA, level of agreement; LoE, level of evidence; RCT, randomised clinical trial; RMD, rheumatic and musculoskeletal disease; TNF, tumour necrosis factor.

Rheumatic and musculoskeletal irAEs occur in a context of cancer; therefore, a dialogue between rheumatologists and oncologists is important to balance the harm and risk of oncology treatment and immunosuppressive drugs. The most important stakeholder is the patient. Shared decision between a patient and his/her rheumatologist is a fundamental principle of RMDs management, as illustrated by its representation as an overarching principle in several European League Against Rheumatism recommendations.[55–57] Because evidence-based data for irAEs management are limited, and irAEs can have a large impact on the quality of life, patient's preferences and discussions concerning risks and benefits of each treatment option are even more important.

C. Rheumatologists should engage with oncologists to contribute to the inter-disciplinary care of patients presenting with musculoskeletal signs and symptoms (LoE na; LoA 9.1).

IrAEs may affect any organ system including the rheumatic and musculoskeletal system. Some patients may even experience multiple organ toxicities in sequence or concurrently. The importance of developing a local multidisciplinary network of oncologists and specialists of all organ system potentially involved in the management of irAEs has been recently highlighted.[58 59] Rheumatologists should actively engage in these local multidisciplinary networks as valuable members due to their knowledge of clinical immunology, their expertise in multiorgan autoimmune disease and their long-standing

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experience with the use of immunosuppressive drugs and biological therapies.[60] This engagement should also include efforts aimed at improving patient education before or when starting cancer immunotherapy, to prevent delay in diagnosis when rheumatic or musculoskeletal side effects occur. Patients have reported that they were informed about other immune-related side effects more than rheumatic or musculoskeletal symptoms.[61] Furthermore, since the rheumatic and the cancer disease both induce high impact on the patient's life, even when independently considered and when disease activity is controlled (ie, fatigue, pain, functional impairments, emotional problems, secondary effects of the treatments), the value of an interdisciplinary collaboration between the rheumatologist and the oncologist is worthwhile.

D. The role of rheumatologists is to assist oncologists in establishing the diagnosis and to relieve rheumatic and musculoskeletal symptoms to an acceptable level enabling patients to maintain effective cancer immunotherapy (LoE na; LoA 9.5).

This principle aimed to better define the role of rheumatologists as oncologists' partners based on the clinical experience of the task force members. Once a patient with cancer receiving immunotherapy is referred for evaluation of rheumatic or musculoskeletal symptoms, the rheumatologist should consider several potential aetiologies: tumour progression, paraneoplastic syndromes, non-rheumatic events (ie, viral infection, thrombosis, endocrine abnormality), all already considered by the referring oncologist, or rheumatic/systemic irAE or immune non-related adverse events. This aspect of differential diagnosis is also described in more detail in recommendation 3. Once a rheumatic irAE is diagnosed, the supervising rheumatologist should propose an appropriate treatment to relieve patient's symptoms to an acceptable level with the objective of maintaining quality of life and permitting continuation of effective cancer immunotherapy, if this is recommended by the oncologist. This treatment goal is different to classic rheumatic entities, in which usually remission is the targeted treatment outcome.

Points to consider

1. Rheumatologists should be aware of the wide spectrum of clinical presentations of rheumatic and/or systemic immune-related adverse events that often do not fulfil traditional classification criteria of RMDs (LoE 4; LoA 9.5).

While arthralgia and myalgia were the most commonly reported rheumatic irAEs in clinical trials, numerous case series and reports have captured a broader spectrum of de novo rheumatic and systemic manifestations that can occur with cancer immunotherapy.[62–64] Polymyalgia rheumatica (PMR)-like syndromes and inflammatory arthritis syndromes are two of the major clinical presentations encountered.[39–41 48 65 66] PMR-like manifestation occurred with a median exposure time to CPI of 60 days, but also much later (IQR 24–210 days). Exposure time to CPI was generally longer for patients experiencing inflammatory arthritis (median 120 days, IQR 48–262 days). In addition, a variety of other rheumatic syndromes have been reported. These include arthralgia; monoarthritis, oligoarthritis or polyarthritis; reactive arthritis; psoriatic arthritis (PsA); remitting seronegative symmetrical synovitis with pitting oedema (RS3PE); tenosynovitis; enthesitis; non-inflammatory musculoskeletal conditions and osteoarthritis.[41 44 46 51 66–77] Importantly, autoantibodies are often absent. In arthritis, only a few patients are positive for rheumatoid factor (RF; n=20, range 18–246 UI/mL) and/or anti-citrullinated peptide antibodies (ACPAs; n=14, range 18–614 U/mL).[78] Instead, positivity of antinuclear antibodies (ANAs) is observed, but often at a low titre (range 1:80 to 1:3200, one patient with ANA 1:12 800 and only 35 patients with ANA >1:160). Similarly, acute phase reactants may be normal in some patients with PMR-like presentations.[41] Overall, around 20% of patients fulfilled classification criteria of rheumatoid arthritis (RA) (55/271) or PMR (11/52). This percentage was higher (55%) for PsA (6/11), as well as in a recent series of PMR-like syndrome (37/49; 75%).[79] The first observation of recurrent pseudogout flares 7 to 10 days after each nivolumab infusion has been recently reported.[80]

Several cases of myositis have been reported, with frequent limb-girdle myalgia and weakness that may mimic a PMR-like condition.[81–83] Because it represents a potentially life-threatening complication, the task force decided to formulate a dedicated recommendation on myositis (*recommendation 8*).

Among systemic manifestations, sicca syndrome has been described early on, presenting mainly with dry mouth, and possible associated neurological symptoms in a few patients.[40 48 65 66 84–87] Two major studies on CPI-induced sicca syndrome were published in 2019 and therefore included in this manuscript. The ImmunoCancer International Registry reported on 26 patients experiencing CPI-associated sicca syndrome. This mainly included men, with frequent organ-specific autoimmune manifestations but lower prevalence of autoantibodies (52% ANA, 20% Ro/SS-A, 9% RF, 8% La/SS-B) in comparison with classical Sjögren's syndrome.[88] Interestingly, a predominant T-cell infiltrate with acinar destruction has been reported in salivary glands, distinct from the histological profile of idiopathic primary Sjögren's syndrome. Authors hypothesise that CPI therapy may break immune tolerance locally leading to the activation of cytotoxic T cells damaging the salivary epithelium.[89]

Other systemic manifestations have been described, including sarcoidosis or sarcoid-like reactions.[90–93] The diagnosis is usually suspected through imaging when new hilar lymphadenopathy or pulmonary nodules are detected in imaging, requiring biopsy. Half of patients experienced cutaneous manifestations (nodules, rash), and some patients had cough/dyspnoea (29%) and arthralgia/arthritis (18%). Uveitis, parotitis, hypercalcaemia and neurological symptoms are rarely reported. Some patients experienced systemic sclerosis or scleroderma-like reactions, all presenting with skin thickening, but only one with new-onset Raynaud's phenomenon.[48 94–96] None tested positive for specific autoantibodies. Since PD-1-deficient mice spontaneously developed lupus-like autoimmune diseases with arthritis and glomerulonephritis, such clinical phenotypes could be expected in patients treated with anti PD-(L)1 agents, but are not observed. A few cases of lupus-like cutaneous reaction and one Jaccoud arthropathy have yet been reported with anti-PD-1 agents, and only one lupus-like nephritis was attributed to anti-CTLA-4 treatment.[97–102]

All vessel-sized vasculitis (eg, large, medium and small vessels) with various clinical manifestations, including purpura, digital necrosis arthralgia, arthritis, myalgia, fever, fatigue and abdominal pain have also been reported.[40 48 84 103–113] Of note, ANA, antineutrophil cytoplasmic antibodies (ANCAs), cryoglobulin and RF were rarely positive. Analysis of the WHO pharmacovigilance database revealed that temporal arteritis (n=16) was particularly over-reported with ipilimumab monotherapy treatment.[114] The first case of granulomatosis with polyangiitis with a high anti-PR3 ANCA titre was reported in 2019.[115]

Recently, patients experiencing rapid bone loss with CPI leading to multiple fractures were reported, raising the question of a potential influence of immune activation on bone metabolism.[116]

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Importantly, rheumatic and/or systemic irAEs may occur across all classes of CPI, most frequently and severely with combination treatments and may be associated with other organ-specific irAEs.

2. Oncologists should be encouraged to consult rheumatologists promptly for assessment when rheumatic musculoskeletal and systemic signs or symptoms are suspected due to immunotherapy, and rheumatologists should provide facilitated access for such patients (LoE 5; LoA 9.4).

The data that are available regarding the process of referral to a rheumatologist suggests that this is not widely done and might lead to delay in diagnosis. In one series, only 4 out of 12 patients experiencing rheumatic irAEs were reviewed by rheumatologists.[43] One cohort reported an average of 9.5±9.3 days between the counselling request and the first rheumatologist visit and 2.5±4.4 months from the start of arthralgias to the confirmation of synovitis.[67] Two other series reported a median of 34 days (range 16–210 days) and 7 days (range 1–57 days) before a rheumatology appointment.[66 117] Rheumatic side effects of CPI appear underappreciated, which probably delays proper assessment and treatment. However, as mentioned in the overarching principles, a prompt rheumatological evaluation should support rapid shared treatment decision to relieve patient symptoms, maintain a good quality of life and allow pursuing an effective cancer immunotherapy.

Currently, algorithms for irAEs management are based on the severity/grade of the irAE according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0). The first international guidelines recommended referral to a rheumatologist in the case of severe symptoms not responding to glucocorticoids (grade 3). Subsequently, prompt referral was proposed as soon as the patient experienced moderate pain associated with signs of inflammation (grade 2).[12–14] While CTCAE grading is routine for oncologists, and a requirement for clinical trials, rheumatologists are less familiar with this grading which do not accurately reflect the spectrum or severity of rheumatic or systemic manifestations (online supplementary table S1). Accordingly, the task force decided not to use the CTCAE grading system to prioritise referral but instead to recommend prompt assessment, ideally before starting glucocorticoids. For this purpose, rheumatologists should be encouraged to offer facilitated access since they may be able to avoid systemic glucocorticoids or use lower dose than oncologists to manage rheumatic toxicities.

3. Metastases, paraneoplastic syndromes and unrelated rheumatic diseases should be considered as a potential differential diagnosis of rheumatic immune-related events. The comprehensive assessment should be focused on documenting evidence of target organ inflammation, and based on history, clinical features, laboratory tests, imaging and/or biopsy (LoE 4; LoA 9.5).

The first part of this statement has previously highlighted the overarching principle of defining the role of the rheumatologist (*overarching principle D*). While delaying the diagnosis of irAEs and its adequate treatment may result in a worse prognosis regarding both CPI adherence and immune-mediated tissue/organ destruction, focusing only on irAEs without considering other differential diagnoses may also be inappropriate. CPIs are commonly administered to patients with advanced cancer, and so new rheumatic/musculoskeletal symptoms must raise suspicion of cancer progression, as well as the lack of improvement of inflammatory arthritis with glucocorticoids (ie, possibility of metastases or paraneoplastic syndrome).[118 119] Advanced imaging, such as CT scan, MRI, bone scintigraphy or positron emission tomography-CT, may be helpful in arriving at such a diagnosis. The diagnosis of irAEs versus metastasis may become even more challenging as non-malignant resorptive lesions have recently been described, which can mimic metastases.[116] Pulmonary sarcoidosis-like lesions may also be first considered as tumour progression.

Immunological toxicities may also manifest as paraneoplastic syndromes. Current literature covers mainly paraneoplastic neurological syndromes with few published data regarding paraneoplastic rheumatic syndromes.[120 121] However, based on the clinical experience of task force members, the group agreed to include paraneoplastic syndromes in the differential diagnosis of rheumatic irAEs to inform clinicians that they may encounter newly and not pre-existing paraneoplastic syndromes following CPI therapy, notably hypertrophic osteoarthropathy. RS3PE and dermatomyositis were also reported, either as paraneoplastic syndromes or induced by CPI therapy, but one may not be able to make the distinction when appearing under CPI therapy.

The term ‘unrelated rheumatic diseases’ covers manifestations for which the causal link with cancer immunotherapy is not obvious, such as shoulder tendinitis, lateral epicondylitis, non-inflammatory back pain or complex regional pain syndrome. The task force agrees that it may be difficult to establish when a specific rheumatic feature can be considered related or unrelated to the administration of CPI. Using the adverse drug reaction probability score (Naranjo scale) may help to assess the causal link with CPI therapy.

The task force proposes that the key objective of the diagnostic work-up is to document evidence of target organ inflammation. By adopting the term target organ inflammation, the task force wants to emphasise that priority for the supervising rheumatologist is not only to search for joint inflammation but also to document evidence of any organ inflammation according to the symptoms presented (muscle, fascia, vessels, heart, lung, skin, endocrine glands, salivary glands, etc), either clinically or preferably by using appropriate laboratory tests, imaging and tissue biopsy.

Tissue diagnosis should be decided on a case-by-case basis, based on the type and severity of rheumatic irAE, when other supportive information would not be sufficient to make a clinical decision in terms of therapy. Notably, histopathological data may be frequently indicated in patients presenting with vasculitis, sarcoidosis and myositis, but should not interfere with starting treatment, particularly with myositis or patients presenting with life-threatening irAE. On the other hand, synovial biopsies will not change the acute management of inflammatory arthritis. They may provide insights into targeted therapies with glucocorticoid saving approaches, but are not recommended for daily practice.

4. In case of inefficacy of symptomatic treatment and depending on the disease severity, local and/or systemic glucocorticoids should be considered for immune-related rheumatic and systemic symptoms. Dose regimen and route of administration should be decided according to the clinical entity and activity. When improvement is achieved, systemic glucocorticoids should be tapered to the lowest effective dose to control the symptoms (LoE 4; LoA 9.4).

In the absence of contraindications, symptomatic treatment including non-steroidal anti-inflammatory drugs and/or analgesics should be the initial treatment for mild-to-moderate rheumatic manifestations. There are no data on the efficacy of symptomatic therapies in the context of systemic manifestations. An anti-inflammatory effect of these drugs can be expected within several hours or a few days. Additionally, intra-articular glucocorticoids should be considered in the context of monoarthritis

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or oligoarthritis, combined with an analysis of the synovial fluid, whenever possible, to rule out differential diagnoses such as infection, osteoarthritis or crystals.[40–42 48 66 67 75–77 122–126] If symptomatic treatment is insufficient and tissue inflammation is still evident, systemic glucocorticoids should be considered for both immune-related rheumatic and systemic symptoms. Overall, systemic glucocorticoids were used for 224/296 patients (76%) with arthritis[39–44 46 48 51 52 65–74 76–78 83 116 122 123 125–143] with a median dosage of 20 mg/day, for 37/65 patients (57%) with sicca syndrome[39 40 65 66 85–89] with a median dosage of 40 mg/day (16 patients for sicca symptoms, 15 patients for systemic manifestations or associated arthritis, 6 patients for sicca symptoms and associated other irAE), for 22/29 patients (76%) with vasculitis[48 84 103–106 108–112 144–150] with a median initial dosage of 60 mg/day, for 15/33 patients (45%) with sarcoidosis[39 44 91–93 151–158] with a median initial dosage of 55 mg/day, for 7/7 patients (100%) with scleroderma[48 94–96] with an initial dosage of 1 mg/kg/day and for 4/13 patients (31%) with lupus.[98–101] Subacute cutaneous lupus was mainly treated with topical steroids.[97] Treatment of patients with myositis is reported in a separate statement (*point to consider 8*).

So far, there are reassuring data regarding the use of glucocorticoids for irAE management.[159 160] For rheumatic irAEs, patients receiving glucocorticoids equivalent to 10 mg/day of prednisolone for 6 weeks concurrent to anti-PD1 therapy had a similar antitumour response.[77] However, recent preclinical data point out that glucocorticoids markedly impair the activation and the killing ability of tumour-infiltrating lymphocytes.[161] Because of concerns of glucocorticoids on antitumour responses, the task force did not recommend using methylprednisolone pulses or high-dose oral glucocorticoids in the absence of life-threatening complications and myositis, even in severe presentations, and favoured the concept of glucocorticoid sparing where rheumatologists have extensive experience with alternative options. Furthermore, the task force members recommended tapering glucocorticoids to the lowest effective dose within weeks or as soon as improvement is achieved was desirable. The objective of reaching a dose less than or equal to 10 mg/day of equivalent prednisone was considered as an acceptable target dose. This target dose as maintenance therapy is based on current preclinical and retrospective clinical data,[161–163] and higher than the one recommended for the main classical RMDs (online supplementary table S2).

5. csDMARD should be considered in patients with insufficient response to acceptable dose of glucocorticoids or requiring glucocorticoid-sparing (LoE 4; LoA 9).

In case of active rheumatic irAE requiring dose of glucocorticoids higher than 10 mg/day of equivalent prednisone, conventional synthetic disease-modifying antirheumatic drug (csDMARD) should be considered. Several csDMARDs have been used as second-line therapy in the case of an insufficient response to glucocorticoids or for use as steroid sparing agents. So far, no specific biological disease-modifying antirheumatic drug has proven superiority. For the various types of arthritis in cases reported, methotrexate was the most frequently drug prescribed, followed by hydroxychloroquine then sulfasalazine, either as monotherapy or in combination.[39–41 43 44 48 51 52 65–67 69 70 75–78 122 123 125 128 131 132 134 140–142 164 165] Of note, no safety issues were described regarding long-term use of methotrexate associated with CPI in a few patients, with a median follow-up of over 1 year.[67] It is noteworthy that a higher proportion of hypersensitivity reactions were reported with sulfasalazine in the context of CPI-induced inflammatory arthritis, suggesting caution to its use in those situations.[165] One case series reported the initiation of hydroxychloroquine prior to glucocorticoids, limiting glucocorticoid exposure, which would deserve further evaluation.[166] The use of csDMARDs has not been described for patients with CPI-induced sicca syndrome. Two patients received hydroxychloroquine and one the combination of hydroxychloroquine and methotrexate for cutaneous leucocytoclastic vasculitis.[103] One patient with granulomatosis with polyangiitis was treated with oral cyclophosphamide.[105] For other systemic manifestations, hydroxychloroquine was safely prescribed for patients with CPI-induced lupus and scleroderma and in one patient with sarcoidosis.[48 95–100 157] Four patients with scleroderma-like syndromes received mycophenolate mofetil.[48 94 96] Among them, two also received intravenous immunoglobulin. Finally, two patients with neurosarcoidosis were successfully treated with methotrexate after an infusion reaction to infliximab.[92 93]

6. For patients experiencing severe rheumatic and systemic immune-related adverse events or with insufficient response to csDMARD, bDMARD may be considered, with TNF or IL-6 inhibitors being the preferred options for inflammatory arthritis (LoE 4; LoA 8.8).

Gastroenterologists have safely and successfully administered infliximab for patients with severe CPI-induced colitis who had an insufficient response to glucocorticoids.[167 168] Based on these data, tumour necrosis factor (TNF) inhibitors (infliximab prevailing on etanercept and adalimumab) have been reported for severe and refractory inflammatory arthritis.[65 66 116 123 138] However, while patients experiencing colitis required one or two infliximab infusions, patients with arthritis may require long-term administration of TNF inhibitors, which is an important difference of unclear clinical significance at this time. A recent study reported that antitumour responses were not adversely affected in patients treated with TNF inhibitors, with a median follow-up of 9 months, but further data are needed.[169] Preclinical data support the use of TNF inhibitors, since infliximab only had a minor influence on T-cell activation and the killing ability of tumour-infiltrating lymphocytes, whereas even low doses of glucocorticoids markedly impaired this antitumour activity.[161] Furthermore, a synergistic effect of TNF inhibitors with CPI has been demonstrated in mouse models.[170 171] A phase I investigator-initiated trial (TICIMEL, NCT03293784) is currently testing the safety of this combined approach (double immunotherapy plus TNF inhibitor) in patients with melanoma. Results of this study will likely inform the management of rheumatic irAEs. The use of infliximab was also reported in two patients with neurosarcoidosis.[92 93]

There are also several observations in patients with CPI-induced inflammatory arthritis treated with tocilizumab.[48 52 68 83] Notably, one patient responded to tocilizumab after infliximab failure.[52]

Regarding interleukin 17 blockade, the use of secukinumab has been reported in a patient with mismatch-repair-deficient metastatic colon cancer and a previous history of Crohn's disease who experienced colitis, severe psoriatic rash and arthralgia.[172] While providing a dramatic relief of the immune-related skin, rheumatic and gastrointestinal side effects, subsequent tumour progression was observed. A second recent publication described the complete resolution of pembrolizumab-induced psoriasiform eruption with secukinumab in a patient with melanoma, without impact on tumour response.[173] Due to limited data and concerns about interleukin 17 inhibition on CPI efficacy, the task force agreed not to recommend interleukin 17 blockade for inflammatory arthritis.

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For mechanistic reasons, abatacept should also not be considered for the treatment of CPI-induced rheumatic and systemic diseases, owing to the hypothetical risk of antagonising antitumour responses of CPI. However, one may consider its use in cases of life-threatening conditions, as discussed in the statement for myositis (*point to consider 8*).

One patient with neuro-Sjögren's syndrome was successfully treated with rituximab after intravenous pulses of methylprednisolone, immunoglobulins and one dose of cyclophosphamide.[87] Rituximab was also used in one patient with acral vasculitis without improvement and the need of surgical amputation.[105]

7. The decision to hold or to continue the cancer immunotherapy should be based on the severity of rheumatic immune-related adverse events, the extent of required immunosuppressive regimen, the tumour response and its duration, as well as the future oncology treatment plan, in a shared decision with the patient (LoE 5; LoA 9.4).

Currently, decisions regarding CPI and immunosuppressive regimens vary from institution to institution according to local practice, with no randomised trials to provide evidence in choosing between holding CPI and/or introducing an immunosuppressive regimen. Overall, the SLR revealed that CPIs were discontinued in 25% of patients experiencing inflammatory arthritis, 61% of patients with sicca syndrome (a discontinuation of CPI often due to another associated irAE), 80% of patients with vasculitis, 64% of patients with sarcoidosis, 75% of patients with scleroderma and 78% of patients with lupus. It is noteworthy that several studies reported ongoing clinical benefit in patients who discontinue their cancer immunotherapy for irAEs.[7 174 175] Well-designed prospective trials will be required help to clarify the optimal immunosuppressive regimens.

8. Myositis may be a severe condition. Immunotherapy withdrawal needs to be discussed. In the presence of life-threatening manifestations (bulbar symptoms (dysphagia, dysarthria, dysphonia), dyspnoea and myocarditis), high dose of glucocorticoids, IVIg and/or plasma exchange should be considered; immunotherapy withdrawal is always necessary (LoE 4; LoA 8.9).

Myositis belongs to the spectrum of potentially fatal toxicity associated with CPI, since it is frequently associated with myocarditis and/or myasthenia gravis.[176–178] Notably, it generally occurs very early after CPI initiation, often within the first month of treatment (median exposure time of 25 days, IQR 25–45 days). Proximal weakness and myalgia are the major symptoms, which can mimic a PMR-like condition.[81] Therefore, a high awareness for myositis is needed among rheumatologists with measurement of creatine kinase (CK) since increased CKs are seen in the majority of patients with myositis (median of 2650 IU/L, ranging from 335 to 20 270 IU/L).[48 77 81–83 100 117 179–207] Of note, CK levels are usually within the normal range in patients presenting with myalgia.[42 83] Ptosis and diplopia are also commonly reported and may be related to associated myasthenia gravis.[81 82 100 117 184 185 189 191 192 195 197 198 204 205 208–210] Of note, some patients present with dropped head syndrome.[82 198 211] Importantly, one should search for the presence of life-threatening manifestations, including dyspnoea, palpitations, chest pain or syncope, which should alert on a possible concurrent myocarditis.[39 48 77 81–83 117 177–179 182 184 185 187 190 193 200 207 211–215] Of note, an increased risk of death in patients experiencing CPI-related myositis has been observed compared with patients with idiopathic inflammatory myositis (around 20% vs less than 10%).[177 216] This increased mortality rate seems to be related to the development of myocarditis. While there is no standardised assessment of myocarditis in large series of idiopathic inflammatory myopathy, signs of myocardial inflammation cardiac has been reported on magnetic resonance tomography in more than 60% of such patients,[217] which argue that myocarditis belong to the myositis clinical spectrum and does not represent a different concomitant irAE. Therefore, cardiac evaluation must be systematic for any patient with myositis or suspected myositis. It includes cardiac troponin (troponin T is less specific than troponin I in case of associated skeletal muscle diseases) and electrocardiography. In case of clinical syndrome associated with myocarditis and/or increase cardiac troponin level and/or electrocardiography, a cardiac MRI is necessary.[218] Of note, normal cardiac enzyme cannot always rule out the possibility of myocarditis. Furthermore, the presence of bulbar symptoms (dysphagia, dysarthria, dysphonia) and/or respiratory failure may be related to myositis or associated myasthenia gravis encountered in 12.5% of patients (57/454 cases reported).[82 83 100 177 178 186 188 189 192 195 203 204 208 211 212] Of note, the majority of patients will not have a typical skin rash of dermatomyositis, only reported in a few patients.[199 201 219]

Myositis-associated autoantibodies are mostly negative, though cases with positive ANA, antistriated antibodies, anti-PM/Scl, anti-SM, anti-TIF1 gamma, anti-PL-7, anti-PL12, anti-Jo1 or anti-SRP have been reported.[77 83 117 184] Electrodiagnostic studies usually reveal myopathic pattern with musculature enhancement may be observed on MRI. Biopsy is often performed and confirms muscle damage with variable degrees of inflammatory and necrotic changes.[81] Of interest, fasciitis is also increasingly reported clinically and seen on MRI findings.[40 76 220–224]

Prompt recognition and early management of myositis is imperative. Discontinuation or at least interruption of CPI was reported in more than 85% of patients and is mandatory in the presence of dyspnoea, bulbar symptoms, severe muscle weakness and/or myocarditis. High-dose systemic glucocorticoids are the first-line treatment, usually 1–2 mg/kg/day (median dosage 70 mg/day). Ten per cent of reported patients received intravenous pulses of methylprednisolone. Up to 20% of patients also received intravenous immunoglobulins,[39 48 77 81–83 181 183–185 188 189 191 198 201 207–209 211 212 220 225 226] and plasma exchanges were performed in around 10% of patients.[48 81 82 117 150 184 188 189 191 197 204 205 226] As second-line therapy, several csDMARDs have been used: mycophenolate mofetil,[77 209 225] methotrexate,[39 44 77 81] azathioprine in one patient but stopped for pancreatitis[77] and hydroxychloroquine in one patient.[76] Six patients have been treated with infliximab, but only one successfully.[82 182 184 225] Importantly, a recent publication reported the resolution of a severe glucocorticoid-refractory myocarditis with abatacept, received after plasma exchanges was unsuccessful.[227] Another T-cell directed therapy, alemtuzumab, has been successfully used in a patient with glucocorticoid-refractory myocarditis.[228] The task force agreed that further evaluation is warranted, most notably on the impact on tumour response; however, due to the lack of effective therapy and the high mortality rate of myositis complicated with myocarditis or severe respiratory failure, one may consider their use as rescue therapy in refractory situations.

9. A pre-existing autoimmune rheumatic and/or systemic disease should not preclude the use of cancer immunotherapy. Baseline immunosuppressive regimen should be kept at the lowest dose possible (for glucocorticoids, below 10 mg prednisone per day if possible). However, many patients may have a flare of the underlying condition and/or immune-related adverse events, requiring the use of glucocorticoids and/or DMARDs (LoE 4; LoA 9).

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Patients with pre-existing inflammatory or autoimmune disease have been largely excluded from clinical trials due to the theoretical risk of worsening autoimmune manifestations. However, there are several series reporting on CPI safety in such patients, with either anti-CTLA-4[229–231] or anti-PD-(L)1 .[77 232–235] Together, a flare of the pre-existing inflammatory or autoimmune disease was observed in half of patients with RA (47/86 patients), PsA (4/8 patients) and myositis (1/2 patients), 64% of patients with PMR (16/25 patients), 31% of patients with SA (4/13 patients) and patients with systemic lupus erythematosus (4/13 patients), 43% of patients with Sjögren's syndrome (3/7 patients), 25% of patients with systemic sclerosis (2/8 patients) and 20% of patients with sarcoidosis (3/15 patients), but less than 10% had to stop CPI therapy during a flare. The patient with pre-existing giant cell arteritis experienced a relapse. There was no flare reported for the few patients with pre-existing seronegative arthritis (n=4), other vasculitis (n=4) and Behçet's disease (n=1). Furthermore, 18 of 104 patients (17%) experienced other irAEs, mainly colitis (n=12), hypophysitis (n=3) and thyroiditis (n=3). One patient with RA developed myositis requiring high dose of glucocorticoids and intravenous immunoglobulins, and another patient with RA developed Sjögren's syndrome with autoantibodies (ANA 1/1280, anti-SSA and SSB). Overall, CPI was discontinued in 8% of patients with pre-existing autoimmune disease due to other irAEs, unrelated to their pre-existing autoimmune disease. In a recent case series of 112 patients with pre-existing autoimmune diseases treated with CPI, a flare of pre-existing autoimmune disease or another irAE occurred in 71% of the patients (47% has a flare of their pre-existing disease and 43% had another irAE).[236] Thus, the occurrence of a flare/irAE was frequent but mostly manageable without CPI discontinuation in 79% of the patients.

In these case series, most flares and irAEs were managed with glucocorticoids, with the need of csDMARDs in some patients, usually hydroxychloroquine, methotrexate, sulfasalazine, either in monotherapy or in combination. The need for TNF inhibitors was only reported in patients with flares of their inflammatory bowel disease flares and in two cases of new-onset colitis. Based on these data, the task force agreed that CPI therapy in patients with pre-existing autoimmune rheumatic and systemic disease was not contraindicated, provided that the patient is well-informed and closely monitored. No preventive treatment is needed. Importantly, this remains a shared decision between the oncologist, rheumatologist and the patient, and whether CPI will be used in a metastatic or adjuvant setting is a major aspect to be considered.

Regarding baseline immunosuppressive regimen, recent preclinical and clinical data highlighted the deleterious impact of baseline glucocorticoids on CPI efficacy, when used at a dosage of greater than 10 mg/day.[163 237] However, this was in patients treated with steroids for their cancer or cancer-related symptoms and not for autoimmune symptoms. Accordingly, the task force agreed on recommending the lowest immunosuppressive regimen possible at the start of CPI therapy. However, future data on prophylactic TNF inhibition and a possible synergistic effect of TNF inhibitors and CPI, reported in a mouse model and currently evaluated in patients, may challenge this statement over time.[171]

10. Before initiation of cancer immunotherapy, there is no indication to test every patient for the presence of autoantibodies. In the case of unexplained rheumatic, musculoskeletal or systemic symptoms, a complete rheumatologic assessment should be performed (LoE 5; LoA 9).

Analysis of pretreatment and post-treatment sera of anti-CTLA4-treated patients with melanoma revealed that for most autoantibodies, including RA-associated antibodies, post-treatment titres increased only marginally and were not associated with the occurrence of irAEs.[238] Similarly, the presence of ANA in serum collected prior to initiating CPI therapy was not found to predict the development of irAEs, except for colitis.[239 240] One study reported divergent data, with pre-existing antibodies independently associated with the occurrence of irAEs, but also with clinical benefits on advanced non-small cell lung cancer.[241] Notably, skin reactions were more frequent among patients with pre-existing RF.

Since autoantibodies are not found in the majority of patients experiencing CPI-induced rheumatic and systemic disease, there is no indication to test every patient at baseline. Of note, the presence of ACPAs has been detected in serum samples obtained prior to CPI therapy in few patients who experienced RA and were asymptomatic before the start of CPI.[78] But this situation might be rare, and the detection of autoantibodies in an asymptomatic patient would not preclude the start of CPI therapy. However, there is the particular situation of patients with thymoma who develop CPI-induced myositis and who all have anti-acetylcholine receptor and antistriated muscle antibodies detected in serum sample obtained prior to CPI therapy.[179] Accordingly, as myositis may evolve into a severe irAE, testing for the presence of these antibodies before starting CPI in a patient with thymoma is recommended to identify a high risk of myositis.

CONCLUSION

These points to consider provide the basis of an European League Against Rheumatism consensus on the diagnosis and the management of rheumatic and systemic irAEs which represent a new and rapidly expanding field. The task force aimed to raise awareness and to assist rheumatologists to improve the diagnosis and the management of patients with irAEs. In contrast to other irAEs, rheumatic irAEs frequently persist over time, specifically inflammatory arthritis was persistent in almost 50% at most recent follow-up with a median of 9 months in a recent study.[169] Thus, irAEs represent a new spectrum of RMDs that rheumatologists should familiarise with. Interestingly, many of these manifestations, either frequent (arthritis, myositis, sicca syndrome) or more exceptionally reported (scleroderma, lupus) are also characteristics of graft versus host disease.[242] Early consultation and strong collaboration between the referring oncologist, the treating rheumatologist, potentially other organ specialists and the patient are all required for optimal irAEs management.

These statements, being based almost entirely on low levels of evidence and on experts opinion, will undoubtedly require updating over the next few years, as new data emerge. Indeed, we expect that future oncological data will likely impact our irAEs therapeutic strategy. We also anticipate a better understanding of irAEs mechanisms and pathophysiology. Finally, multicentre collaborative efforts, prospective registries and randomised trials will help to define the optimal treatment strategies to relieve patient symptoms without altering oncological outcomes.

RESEARCH AGENDA

- To better understand pathophysiology of rheumatic and systemic irAEs.
- To develop information on rheumatic and systemic irAEs for patients starting cancer immunotherapy.
- To define optimal glucocorticoid dose and duration according to the type of rheumatic and/or systemic irAE.
- To assess the effect of different immunomodulatory/immunosuppressive agents already given before the start

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of CPI therapy in pre-existing RMDs on the outcome of immunotherapy.
- To assess the effect of different immunomodulatory/immunosuppressive agents administered for de novo rheumatic and systemic irAEs on the outcome of immunotherapy, using prospective registries.
- To develop well-designed trials on irAE management.
- To assess long-term evolution of rheumatic and systemic irAEs.
- To search for predictive factors for rheumatic and systemic irAEs.
- To revise CTCAE grading of rheumatic and systemic irAEs.
- To obtain insights on the initiation and propagation of classical rheumatic diseases.

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Acknowledgements The task force gratefully thank the librarian Catherine Weill (Bibliothèque Inter-universitaire de Santé, Paris, France) for her contribution to the systematic literature search, and European League Against Rheumatism for financial and logistical support.

Contributors The paper was drafted by MK, XM, AF and TS and all authors contributed with specific comments and revisions to the paper.

Funding This study was funded by European League Against Rheumatism (grant no: CLI106).

Competing interests MK: honoraria from Abbvie, BMS, Lilly, Novartis, Pfizer; TRDJR: grants from AbbVie, Takeda, UCB, Janssen, GSK and honoraria from Abbvie, Pfizer, Takeda, Lilly, Medimmune, Novartis, GSK, BMS, AstraZeneca, Janssen; XM: honoraria from BMS; COB: grants and honoraria from BMS and honoraria from Genetech/Roche, Sanofi/Regeneron; OL: grant from Gilead and honoraria from BMS, MSD, AstraZeneca, Janssen; JLe: grants from Novartis, Pfizer and honoraria from Abbvie, AstraZeneca, BMS, Celgene, Hospira, Janssen-Cilag, LEO Pharma, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, UCB; AM: grants from BMS, Merus and honoraria from Merck Serono, Lytix, BMS, Symphogen, Amgen, AZ/Medimmune, Servier, Gritstone, Pierre Fabre, EISAI, Sanofi; TS: honoraria from Pfizer, Lilly, Novartis, BMS, Abbvie, Sanofi; EHC: grants from Biogen, grants and honoraria from Amgen, Bio-Cancer, Roche, UCB, Pfizer, honoraria from Chugai Pharma, Abbvie, BMS, Celgene, Eli Lilly, Janssen, ObsEva, Regeneron, Sanofi, SynAct Pharma, Tonix, Gilead; LT: honoraria from Novartis; KB: grants from Abbvie, Novartis, Rheumaliga Baden-Württemberg and honoraria from MSD, Abbvie, BMS, Janssen, Lilly, Mundipharma, Novartis, Pfizer, Roche, UCB; KV: speaker fees from BMS; JLa: grants from Aveo and Pharmacyclics, grants and honoraria from Achilles Therapeutics, MSD, Nektar, Novartis, Pierre Fabre, Pfizer, Roche/Genetech and Immunocore, honoraria from AstraZeneca, Boston Biomedical, BMS, Eisai, EUSA Pharma, GSK, Ipsen, Imugen, Incyte, iOnctura, Kymab, Merck Serono, Secarna, Vitaccess and Covance; JBAGH: grants from BMS, Novartis and advisory boards and/or lectures for MSD, BMS, Roche, Novartis; J-EG: grants from BMS, UCB, Pfizer, Sanofi and honoraria from BMS, Lilly, Pfizer, Sanofi-Genzyme, UCB.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information

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Rheumatology 2006;45:1039–1041
Advance Access publication 6 July 2006
doi:10.1093/rheumatology/kel163a

Guidelines

BSR & BHPR, BOA, RCGP and BSAC guidelines for management of the hot swollen joint in adults

G. Coakley[1], C. Mathews[1], M. Field[2], A. Jones[3], G. Kingsley[4], D. Walker[5], M. Phillips[6], C. Bradish[7], A. McLachlan[8], R. Mohammed[9] and V. Weston[10], on behalf of the British Society for Rheumatology Standards, Guidelines and Audit Working Group

KEY WORDS: Septic arthritis, Guidelines, Management.

Scope and purpose of the guidelines

The clinical presentation of a hot swollen joint is common and has wide differential diagnosis. The most serious is septic arthritis, with a case fatality of 11%. Delayed or inadequate treatment leads to joint damage. These guidelines focus on the diagnosis and management of septic arthritis. Hot swollen joints commonly have other underlying diagnoses, including crystal arthritis, reactive arthritis and a monoarticular presentation of polyarthritis.

Guidelines for managing the hot swollen joint in adults

The guidelines have been developed for use with adults who develop a hot swollen native joint acutely (typically with a history of two weeks or less) affecting any joint except the axial skeleton. This is an abridged version, which is available in full as supplementary material on the journal website.

Symptoms and signs suggestive of septic arthritis

(1) Patients with a short history of a hot, swollen and tender joint (or joints) with restriction of movement should be regarded as having septic arthritis until proven otherwise (B).
(2) If clinical suspicion is high, then it is imperative to treat as septic arthritis even in the absence of fever (B).

Investigation of synovial fluid

(1) The synovial fluid must be aspirated, Gram-stained and cultured prior to starting antibiotics (B). Warfarin does not contraindicate needle aspiration (C).
(2) A possibly infected prosthetic joint should always be referred to an orthopaedic surgeon (C).
(3) Neither the absence of organisms on Gram stain nor a negative subsequent synovial fluid culture excludes the diagnosis of septic arthritis (B).
(4) Specimens must be sent fresh to the laboratory and obtained prior to starting antibiotics (C).
(5) Polarising microscopy should always be carried out (B).

Other laboratory investigations

(1) Blood cultures should always be taken (B).
(2) The white cell count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be measured (B). Inflammatory markers are useful for monitoring response to treatment (B).
(3) The serum urate level is of no diagnostic value in acute gout or sepsis (B).
(4) Electrolytes and liver function should be measured to detect end organ damage because renal function may influence antibiotic choice (B).

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Submitted 13 March 2006; revised version accepted 4 April 2006.

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(5) If the history suggests non-articular infection, then appropriate cultures and swabs should be taken prior to starting antibiotics (B).

Imaging

Plain radiographs of the affected joint are of no benefit in diagnosing septic arthritis but may show chondrocalcinosis. They should be performed as a baseline investigation (C).

Magnetic resonance imaging is the most appropriate imaging where required, since it is sensitive in detecting osteomyelitis that may require a surgical approach (B).

In suspected hip sepsis, diagnostic aspiration will usually require the use of ultrasound or an image intensifier (C).

Antibiotic treatment of septic arthritis

There is no evidence on which to advise the optimal duration of i.v. or oral antibiotics. Conventionally, they are given intravenously for up to 2 weeks or until signs improve, then orally for 4 weeks. Symptoms, signs and acute phase responses are all helpful in guiding the decision to stop antibiotics. Expert review may be required if the expected resolution does not occur (C).

Summary of recommendations for initial empirical antibiotic choice in suspected septic arthritis

Patient group	Antibiotic choice
No risk factors for atypical organisms	Flucloxacillin 2 g qds i.v. Local policy may be to add gentamicin i.v. If penicillin allergic, clindamycin 450–600 mg qds i.v. or 2nd or 3rd generation cephalosporin i.v.
High risk of Gram-negative sepsis (elderly, frail, recurrent UTI, and recent abdominal surgery)	2nd or 3rd generation cephalosporin eg cefuroxime 1.5 g tds i.v. Local policy may be to add flucloxacillin i.v. to 3rd generation cephalosporin. Discuss allergic patients with microbiology—Gram stain may influence antibiotic choice
MRSA risk (known MRSA, recent inpatient, nursing home resident, leg ulcers or catheters, or other risk factors determined locally)	Vancomycin i.v. plus 2nd or 3rd generation cephalosporin i.v.
Suspected gonococcus or meningococcus	Ceftriaxone i.v. or similar dependent on local policy or resistance
i.v. drug users	Discuss with microbiologist
ITU patients, known colonisation of other organs (e.g. cystic fibrosis)	Discuss with microbiologist

Note: antibiotic choice will need to be modified in light of results of Gram stain and culture. This table is based on expert opinion and should be reviewed locally by microbiology departments. UTI, urinary tract infection; MRSA, methicillin-resistant *Staphylococcus aureus*; ITU, intensive therapy unit.

Joint drainage and surgical options

(1) Septic joints should be aspirated to dryness as often as required (C).
(2) This can be done either through a closed-needle approach or arthroscopically according to local preferences (C).
(3) If the response is not satisfactory with a closed-needle approach, arthroscopic aspiration should be used (C).
(4) In suspected hip sepsis, arrange early referral for an orthopaedic opinion. Urgent open debridement is often necessary (C).

Recommendations specific to primary care and the Emergency Department (ED)

(1) The commonest hot joint to present in primary care is the great toe metatarsophalangeal joint. This is almost always due to gout and can be diagnosed on clinical grounds (B).
(2) Some general practitioners (GPs) regularly aspirate and inject joints. If they aspirate unexpected cloudy fluid from a joint, they should send the sample with the patient to the ED and not inject corticosteroid (C).
(3) GPs and ED doctors should refer patients with suspected septic arthritis to a specialist within the hospital who has the expertise to aspirate the joint (C).
(4) Patients should be admitted to hospital if sepsis is suspected (C).
(5) If there is doubt about whether sepsis might be present, intra-articular steroids should not be used (C).
(6) The skills necessary to aspirate a joint in hospitals will commonly be held by specialists and trainees in ED, orthopaedics and rheumatology (C).

Mechanism for audit of the guidelines

In cases of proven septic arthritis:

(1) Was the joint aspirated at presentation prior to antibiotics? If not, what was the reason?
(2) Was there a delay in treatment and, if so, why?
(3) Was ESR and CRP measured at diagnosis and serially?
(4) Were appropriate cultures taken?
(5) Was the initial antibiotic choice in keeping with the guidelines?
(6) Was prosthetic joint sepsis managed by orthopaedic surgeons?

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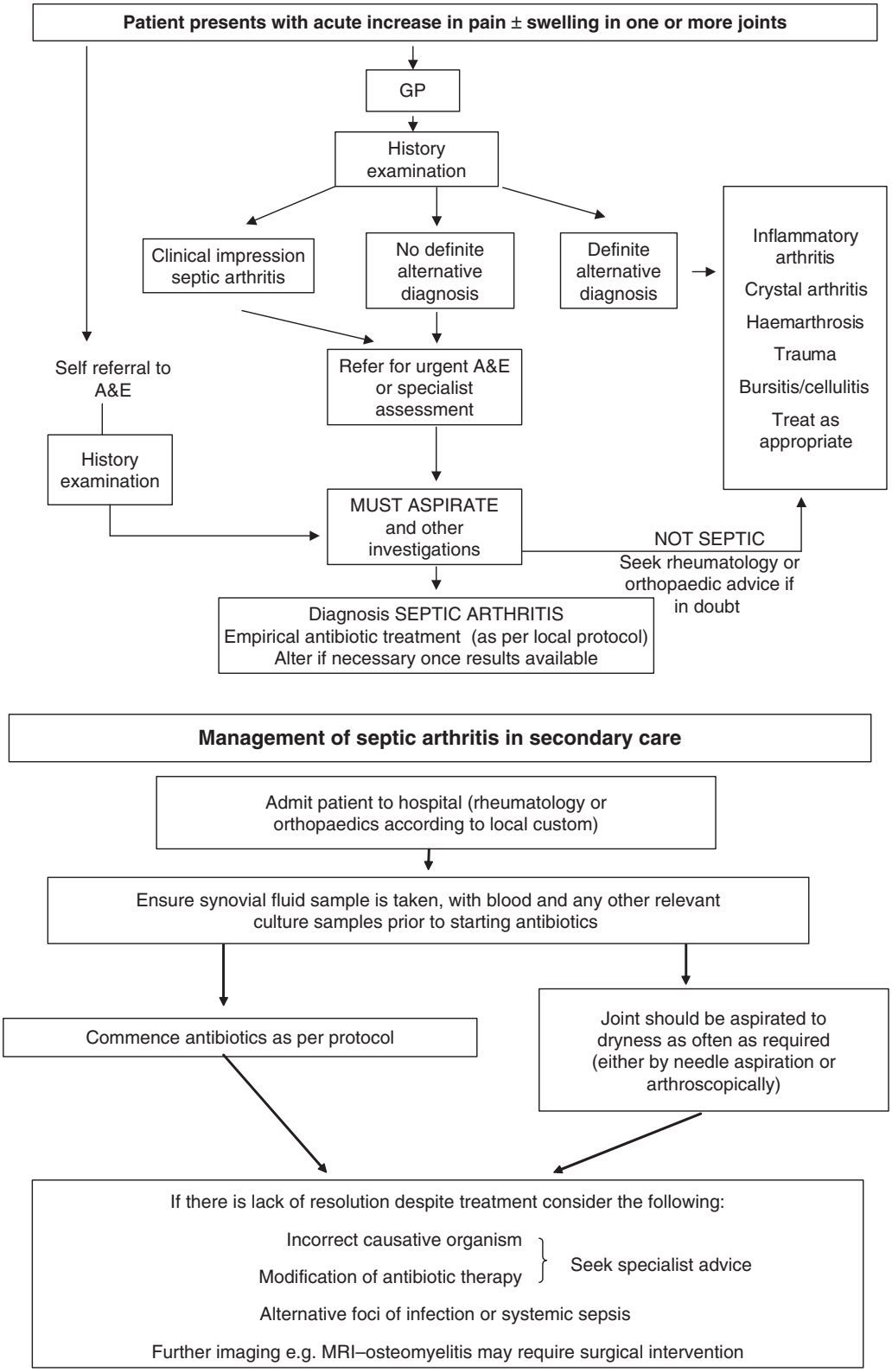
Algorithm of guidelines


Patient presents with acute increase in pain ± swelling in one or more joints
GP
History examination
Clinical impression septic arthritis
No definite alternative diagnosis
Definite alternative diagnosis
Inflammatory arthritis
Crystal arthritis
Haemarthrosis
Trauma
Bursitis/cellulitis
Treat as appropriate
Self referral to A&E
Refer for urgent A&E or specialist assessment
History examination
MUST ASPIRATE and other investigations
NOT SEPTIC
Seek rheumatology or orthopaedic advice if in doubt
Diagnosis SEPTIC ARTHRITIS
Empirical antibiotic treatment (as per local protocol)
Alter if necessary once results available
Management of septic arthritis in secondary care
Admit patient to hospital (rheumatology or orthopaedics according to local custom)
Ensure synovial fluid sample is taken, with blood and any other relevant culture samples prior to starting antibiotics
Commence antibiotics as per protocol
Joint should be aspirated to dryness as often as required (either by needle aspiration or arthroscopically)
If there is lack of resolution despite treatment consider the following:
Incorrect causative organism
Modification of antibiotic therapy
Seek specialist advice
Alternative foci of infection or systemic sepsis
Further imaging e.g. MRI–osteomyelitis may require surgical intervention

The authors have declared no conflicts of interest.

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